# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-051**

# STATISTICAL REVIEW(S)

# STATISTICAL REVIEW AND EVALUATION

**Biometrics Division: DBVI (HFD-705)**

| | |
|---|---|
| **NDA NO.:** | 22-051 |
| **SERIAL NO.:** | S_001 |
| **DATE REQUESTED:** | August 30, 2006 |
| **DRUG NAME:** | Fluticasone Furoate Nasal Spray |
| **DOSAGE FORM AND STRENGTH:** | Nasal Spray, suspension (27.5 mcg/spray) |
| **SPONSOR:** | Glaxo Group Limited |
| **NAME OF STATISTICAL REVIEWER:** | Meiyu Shen, Ph.D. DBVI (HFD-705) |
| **NAME OF CHEMISTRY REVIEWER:** | Prasad Peri, Ph.D, DPA I |

Meiyu Shen, Ph.D., Mathematical Statistician, DBVI

Concur:

Yi Tsong, Ph.D.
Deputy Director, DBVI

Stella Machado, Ph.D.
Director, DBVI

**Distribution:** NDA 22-051
HFD-705/Y. Tsong, Ph.D.
HFD-705/S.Machado Ph.D.
DPA I/HFD-570/Prasad Peri, Ph.D.
HFD-570/Blair Fraser, Ph.D.
HFD-570/Nashed, Eugenia M, Ph.D.
HFD-570/Jafari, Ladan
Lostritto, Richard T, Ph.D.

## INTRODUCTION

Glaxo Smith Kline proposed an alternative acceptance criterion based on Parametric Tolerance Interval (PTI) Tests for spray weight uniformity, spray content uniformity, and droplet size distribution for the drug product, Fluticasone Furoate Nasal Spray. The conventional tests are the counting procedures, based on the Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation, July 2002. However, the sponsor did not provide detail on exactly how the conventional methods were derived.

Sponsor's alternative acceptance criteria derived from Parametric Tolerance Interval Tests (PTIT) are also provided for key measures of device performance, where

$$L = |100 - \text{Overall Mean}| + k * \text{Overall Standard Deviation}$$

Where the Overall Mean and Standard Deviations are expressed as % of Target label claim.

Each ex-device test is initially performed on 10 devices that yield 20 results. In the event that second tier testing is necessary, an additional 20 devices are sampled to give 60 results in total. Values for the coefficient k are provided in Table 0 for 87.5% and 90.0% coverage and first and second tier sample sizes of 20 and 60 results.

**Table 0 The sponsor's k values**

| Coverage | k | |
|---|---|---|
| | First Tier Testing | Second Tier Testing |
| | n=20 | n=60 |
| 87.5% | — | — |
| 90.0% | — | — |

Here, the sponsor's K values in Table 0 is consistent with that which the Agency developed in conjunction with FDA's efforts with IPAC-RS under PQRI. The sponsor extended the PTI methods for target intervals (L) and coverage for Pump Spray Weight, Spray Content Uniformity and $D_{10}$, $D_{50}$ and $D_{90}$ parameters of the Droplet Size Distribution.

It should be noted that FDA's goalposts are 80-120% of LC, with tier size ratio 1:3, using Pocock distribution of alpha value. They were presented by the Agency in October 2005 at the OPS Advisory Committee meeting (thus pubic domain).

### Pump Spray Weight

Dose Content Uniformity (DCU) is the product of spray weight performance and other characteristics (assay, suspension uniformity, etc.), therefore, more stringent criteria need to be applied to the spray weight test because it has less sources of variability than DCU (which has all of the spray weight issues plus others).

Each determination is the mean weight per spray for a composite sample of two consecutive sprays. Determinations are made at both the beginning and the end of each device.

Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products —Chemistry, Manufacturing, and Controls Documentation, July 2002, stated that in general, pump spray weight delivery acceptance criteria should control the weight of the individual sprays to within 15 percent of the target weight and their mean weight to within 10 percent of the target weight. However, for small dosage pumps (e.g., 20 μL) other acceptance criteria may be justified. It leads to the counting Method (Zero tolerance method) that all determination should be within 15% of the target weight and the mean determination should be within 10 percent of the target weight.

The sponsor proposed an alternative (i.e. sponsor's PTI method) Parametric Tolerance Interval Test with a target interval of [redacted] % coverage in order to assure that at least [redacted] % of sprays delivered from a batch of Fluticasone Furoate Nasal Spray are in the range [redacted] mg. Additionally, the mean results from both the beginning and the end of the 10 or 30 devices must fall within the range [redacted] % of target.

**Spray Content Uniformity**

Spray Content Uniformity was what the PTIT method developed for with regards to inhalation and nasal spray products. This test is designed to demonstrate the uniformity of medication per spray (or minimum dose), consistent with the label claim, discharged from the nasal actuator, of an appropriate number (n = 10 from the beginning and n = 10 from the end) of containers from a batch. The primary purpose is to ensure SCU within the same container and among multiple containers of a batch.

For this test, the sponsor stated that each determination is the mean content of Fluticasone Furoate per spray in a composite sample of two consecutive sprays at both the beginning and end of each device.

In this situation, the sponsor interpreted the counting method in Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products —Chemistry, Manufacturing, and Controls Documentation, July 2002 as follows:

However, alternative approaches (e.g., statistical) can be proposed and used if they are demonstrated to provide equal or greater assurance of SCU.

The sponsor proposed an alternative parametric tolerance interval test with a target interval of % coverage that would assure that at least % of sprays delivered from a batch of Fluticasone Furoate Nasal Spray will contain µg of Fluticasone Furoate.

**Droplet Size Distribution**

The Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products —Chemistry, Manufacturing, and Controls Documentation, July 2002 stated that for both suspension and solution nasal sprays, the specifications should include an appropriate control for the droplet size distribution (e.g., 3 to 4 cut-off values) of the delivered plume subsequent to spraying under specified experimental and instrumental conditions. If a laser diffraction method is used, droplet size distribution can be controlled in terms of ranges for the $D_{10}$, $D_{50}$, $D_{90}$, span $[(D_{90}-D_{10})/D_{50}]$, and percentage of droplets less than 10 µm. Appropriate and validated and/or calibrated droplet size analytical procedures should be described in sufficient detail to allow accurate assessment by Agency laboratories (e.g., apparatus and accessories, calculation theory, correction principles, software version, sample placement, laser trigger condition, measurement range, beam width). In another words, no specific method was recommended in the Guidance.

The sponsor proposed a parametric tolerance interval test with a target interval of and % coverage that would assure at least % of individual sprays delivered from a batch of Fluticasone Furoate Nasal Spray have a $D_{10}$ in the range µm.

$D_{50}$ and $D_{90}$ parameters have shown more variability than $D_{10}$ and it is therefore necessary to widen the target interval to to maintain coverage. This would assure that at least of individual sprays delivered from a batch of Fluticasone Furoate Nasal Spray have a $D_{50}$ in the range µm and a $D_{90}$ in the range µm.

For the evaluation, the statistical reviewer performed a comparison of the PTI procedures proposed by the sponsor and the counting method based on FDA Guidance. The results of the comparison and evaluation are given in the Table 1. The reviewer also performed a comparison of the PTI procedures proposed by the sponsor and by FDA.

## COMPARISON OF THE SPONSOR'S PTI PROCEDURE AND GUIDANCE COUNTING PROCEDURE

Both the sponsor's PTI procedure and Guidance counting method are a two-tier procedure with sample size 20 (10 units and 2 life-stages) at tier 1 and if lot does not pass, an additional 40 values (20 units and 2 life-stages) are evaluated. The details of these two procedures are listed in Table 1.

10 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

MeiYu Shen
3/16/2007 10:23:55 AM
BIOMETRICS

Yi Tsong
3/20/2007 01:13:42 PM
BIOMETRICS

Stella Machado
3/20/2007 01:22:32 PM
BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

# Statistical Review and Evaluation

## CLINICAL STUDIES

| | |
|---|---|
| NDA/Serial Number: | N22-051 |
| Drug Name: | Fluticasone Furoate Nasal Spray 27.5mcg |
| Indication(s): | SAR, PAR in adults and children ages 2 year and older |
| Applicant: | The GlaxoSmithKline group of companies |
| Date(s): | Received 6/28/06; User Fee 4/28/07 |
| Review Priority: | Standard |
| | |
| Biometrics Division: | DB II/Office of Biostatistics |
| Statistical Reviewer: | Feng Zhou, M.S. |
| Concurring Reviewers: | Joy D Mele, M.S. (Acting Statistical Team Leader) |
| | |
| Medical Division: | Division of Pulmonary and Allergy Drug Products (HFD-570) |
| Clinical Team: | Anthony Durmowicz, M.D. (Medical Reviewer)<br>Badrul A Chowdhury, M.D. (Medical Division Director) |
| Project Manager: | Ladan Jafari (HFD-570) |

Keywords: Clinical Studies, NDA review, Dropouts

# Table of Contents

# List of Tables

# List of Figures

# 1. EXECUTIVE SUMMARY

Fluticasone Furoate Nasal Spray 27.5mcg is a new corticosteroid developed by GlaxoSmithKline (GSK), presented as an aqueous suspension in a novel side-actuated nasal spray device for the once daily treatment for symptoms of allergic rhinitis.

The sponsor submitted this application on June 28, 2006 (NDA 22-051) in support of usage in the treatment of nasal symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children 2 years and older.

## 1.1 Conclusions and Recommendations

The efficacy evaluation of four phase-III, randomized, multi-center, double-blind, parallel-group, and placebo-control studies (SAR02, SAR03, SAR04 and PAR01), demonstrated that Fluticasone Furoate Nasal Spray 27.5mcg is statistically significantly superior to placebo in improving the reflective Total Nasal Symptoms Score (rTNSS) after a dosage regimen of two sprays per nostril once daily (100mcg per day, hereafter referred to FF100mcg) in adult and adolescent patients 12 years and older with SAR or PAR. The efficacy evaluation of study SAR01, a phase-II, randomized, multi-center, double-blind, parallel-group, and placebo-control, and dose-finding study, demonstrated that all four dose regimens (50, 100, 200, 400mcg) of FF are statistically significantly superior to placebo in improving the Total Nasal Symptoms Score.

The efficacy of FF100mcg in treating for SAR subjects was supported by the key secondary endpoints of AM pre-dose instantaneous Total Nasal Symptoms Score (iTNSS), daily reflective Total Ocular Symptoms (rTOSS), overall evaluation of response to therapy, and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). For PAR subjects, the treatment difference between FF100mcg and placebo did not reach statistical significance for rTOSS and RQLQ.

The efficacy evaluation of study SAR05, the allergen challenge chamber (ACC) study, did not demonstrate significant onset of action. The onset of action was only observed in two out of four SAR studies at 8 hours after initial administration. In the other two studies, the onset of action was not seen until Hour 24. The improvement in AM pre-dose iTNSS was maintained over the full 24-hour dosing interval.

In children treated with Fluticasone Furoate nasal spray once daily, inconsistent results were observed between the SAR and PAR studies for the 50mcg and 100mcg doses. In SAR study (PED01), children aged 6 to <12 years treated with FF100mcg once daily exhibited statistically significant greater decreases in daily rTNSS than placebo-treated subjects; however, the superiority of FF50mcg over placebo did not reach statistical significance. In PAR study (PED02), children aged 6 to <12 years treated with FF100mcg once daily showed numerically reduced mean daily rTNSS compared with placebo but the difference was not statistically significant. For the FF50mcg dose the reductions in daily rTNSS were statistically significant compared with placebo.

To explore consistency of the treatment effects across the levels of several predefined covariates (age, gender, and race), treatment-by-covariate interactions were evaluated for the primary efficacy endpoint. The results by gender were highly consistent. There were too few patients to examine results for patients 65 and older. Statistically significant results are not expected in all subgroups due to the reduced sample size and natural variation expected when conducting multiple analyses.

### 1.2 Brief Overview of Clinical Studies

**The sponsor's submission included twelve** studies outlined in Table 4 on page 12. Eight of them are adult and adolescent studies and the remaining four are pediatric studies. This reviewer will focus on efficacy studies: SAR01-SAR05, PAR01, PED01, and PED02. Henceforth, the studies are referred to by number as SAR, PAR or PED studies as shown in the table below.

### 1.3 Statistical Issues and Findings

Table 1 summarizes the design and statistical results for the primary efficacy endpoint for the dose-finding, four pivotal, and two pediatric studies. The primary efficacy variable was the mean change from baseline over treatment period of reflective TNSS.

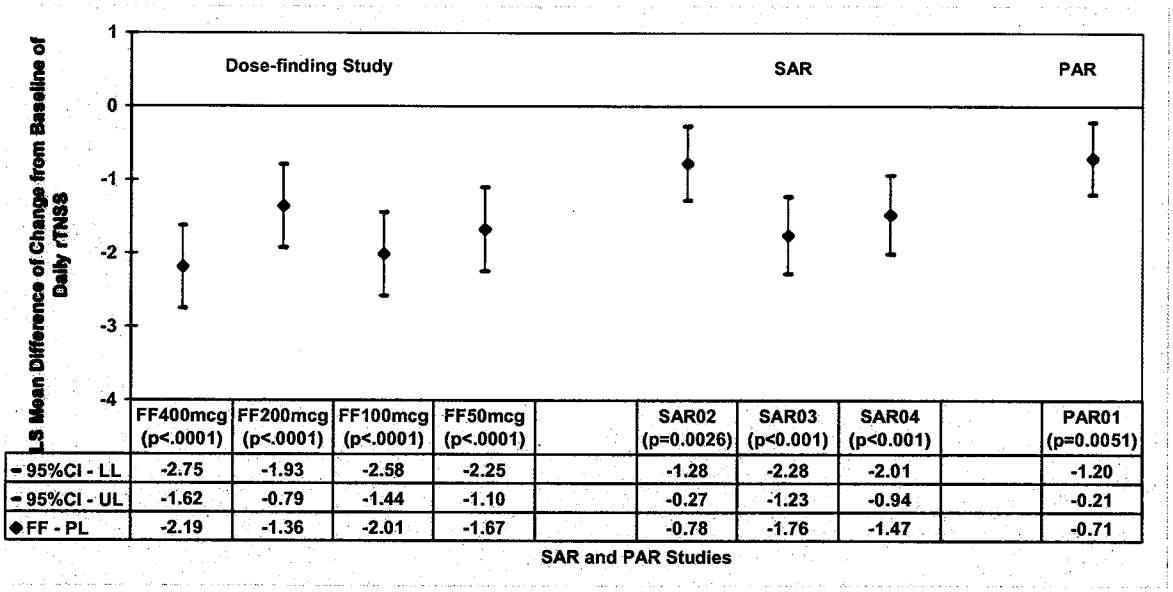
Table 1. Design and Statistical Results of SAR and PAR studies

| ***Study (# of centers, period)*** | ***Treatment groups (N)*** | ***Treatment groups (N)*** | ***LS Mean Difference, (95% CI) (FF – PL)*** |
|---|---|---|---|
| **SAR01**<br>8 centers in Texas, USA<br>2-weeks study<br>**12/2003 – 2/2004** | Age range:<br>**Male: 12 – 80 (220)**<br>**Female: 13 – 75 (422)** | FF400mcg (130)<br>FF200mcg (129)<br>FF100mcg (128)<br>FF50mcg (127)<br>Placebo (128) | 400mcg: **Δ** = -2.19, (-2.75, -1.62)<br>200mcg: **Δ** = -1.36, (-1.93, -0.79)<br>100mcg: **Δ** = -2.01, (-2.58, -1.44)<br>50mcg: **Δ** = -1.68, (-2.24, -1.10) |
| **SAR02**<br>7 centers in US<br>2-weeks study<br>**12/2004 – 1/2005** | Age range:<br>**Male: 12 – 67 (111)**<br>**Female: 13 – 75 (192)** | FF100mcg (152)<br>Placebo (151) | 100mcg: **Δ**= -0.78, (-1.28, -0.27) |
| **SAR03**<br>23 centers in Europe<br>2-weeks study<br>**5/2005 – 8/2005** | Age range:<br>**Male: 12 – 65 (134)**<br>**Female: 14 – 65 (151)** | FF100mcg (141)<br>Placebo (144) | 100mcg: **Δ**= -1.76, (-2.28, -1.23) |
| **SAR04**<br>17 centers in US<br>2-weeks study<br>**8/2005 – 10/2005** | Age range:<br>**Male: 12 – 69 (119)**<br>**Female: 12 – 74 (180)** | FF100mcg (151)<br>Placebo (148) | 100mcg: **Δ**= -1.47, (-2.01, -0.94) |
| **PAR01**<br>47 centers in US/Canada<br>4-weeks study<br>**1/2005 – 5/2005** | Age range:<br>**Male: 12 – 76 (113)**<br>**Female: 12 – 73 (189)** | FF100mcg (150)<br>Placebo (152) | 100mcg: **Δ**= -0.71, (-1.21, -0.22) |
| **PED01**<br>57 centers in US<br>2-weeks study<br>**3/2005 – 11/2005** | Age range:<br>**Male: 2 – 12 (323)**<br>**Female: 2 – 11 (231)** | FF100mcg (184)<br>FF50mcg (184)<br>Placebo (186) | 100mcg: **Δ** = -0.61, (-1.15, -0.08)<br>50mcg: **Δ** = -0.16, (-0.69, -0.38) |
| **PED02**<br>61 centers in 7 countries<br>12-weeks study<br>**2/2005 – 11/2005** | Age range:<br>**Male: 2 – 12 (310)**<br>**Female: 2 – 12 (248)** | FF100mcg (185)<br>FF50mcg (185)<br>Placebo (188) | 100mcg: **Δ** = -0.45, (-0.95, 0.04)<br>50mcg: **Δ** = -0.75, (-1.24, -0.27) |

Data: Demo.xpt. Source code: demo.sas

The primary efficacy results of FF100mcg once daily relative to placebo are shown in Figure 1. For SAR studies and PAR study, the analyses results on primary efficacy endpoint (mean change from baseline in daily rTNSS) showed that FF100mcg once daily was statistically significantly better than Placebo as shown by the 95% confidence intervals for the least squares mean differences being completely below zero (FF - Placebo). The dose-finding study SAR01 demonstrated that FF four dose regimens (50, 100, 200, and 400mcg) are statistically significantly superior to placebo in improving the Total Nasal Symptoms Score.

Figure 1. Primary Analysis of Daily rTNSS for SAR and PAR Adult Studies




***Key Secondary Efficacy Variables***

**Table 2 displays the reviewer's analysis results of the key secondary efficacy variables which** show the efficacy of FF100mcg in treating for SAR subjects was supported by the key secondary endpoints of AM pre-dose iTNSs, daily rTOSS, the Overall evaluation of response to therapy, and RQLQ. For PAR subjects, the treatment difference between FF100mcg and placebo did not reach the statistical significant in rTOSS and RQLQ. The individual nasal symptoms scores, the changes from baseline of daily reflective symptom scores for individual symptoms of the TNSS over 14-days (SAR studies) or 28-days (PAR Study) are summarized in Table 2.

Table 2. The Results of the Secondary Variables for SAR and PAR Studies

| ***Secondary Endpoint*** | ***SAR02 LSM Diff., 95%CI*** | ***SAR03 LSM Diff., 95%CI*** | ***SAR04 LSM Diff., 95%CI*** | ***PAR01 LSM Diff., 95%CI*** |
|---|---|---|---|---|
| ***AM pre-dose iTNSS*** | -0.90 (-1.38, -0.42) | -1.90 (-2.42, -1.38) | -1.38 (-1.90, -0.85) | -0.71 (-1.20, -0.21) |
| ***Daily rTOSS*** | -0.55 (-0.95, -0.14) | -0.74 (-1.14, -0.34) | -0.60 (-1.01, -0.19) | -0.19 (-0.56, 0.17) |
| ***RQLQ*** | -0.69 (-1.08, -0.30) | -0.70 (-0.99, -0.28) | -0.60 (-0.93, -0.28) | -0.19 (-0.54, 0.17) |

| | | | | |
|---|---|---|---|---|
| ***Individual TNSS*** | | | | |
| ***Itchy Nose*** | -0.14, p=0.063 | -0.37, p<.0001 | -0.34, p<0.001 | -0.16, p=0.024 |
| | (-0.28, 0.01) | (-0.52, -0.23) | (-0.45, -0.20) | (-0.30, -0.02) |
| ***Nasal Congestion*** | -0.17, p=0.012 | 09,49, p<0.001 | -0.36, p<0.001 | -0.12, p=0.093 |
| | (-0.30, -0.04) | (-0.63, -0.34) | (-0.50, -0.22) | (-0.27, 0.02) |
| ***Runny Nose*** | -0.21, p=0.004 | -0.48, p<.001 | -0.33, p<0.001 | -0.20. p=0.007 |
| | (-0.35, -0.07) | (-0.62, -0.34) | (-0.48, -0.18) | (-0.34, -0.06) |
| ***Sneezing*** | -0.26, p<0.001 | -0.44, p<.001 | -0.48, p<.001 | -0.23, p= 0.001 |
| | (-0.41, -0.12) | (-0.58, -0.30) | (-0.63, -0.32) | (-0.37, -0.09) |

**Yellow highlight indicates non-significance at alpha=0.05. LSM Diff. = LS Mean of FF100mcg – Placebo**
Blue highlight indicates non-significance at alpha=0.0125. LSM Diff. = LS Mean of FF100mcg - Placebo

***Onset of Action-***

Table 3 summarizes the results of the primary **efficacy analysis – hourly assessment of** instantaneous TNSS on Day 1 and daily assessment of instantaneous TNSS on Day 2, Day 3, Day 4, and Day 5. Two out of four SAR studies (SAR01 and SAR04) demonstrated onset of action at Hour 8 and all four SAR studies (SAR02 and SAR03) demonstrated the onset of action **at 24 hours. The ACC study didn't show the onset of action at any time point.**

Table 3. Hourly Assessment of iTNSS on Day1- Day 5 (LS Mean FF100-Placebo)

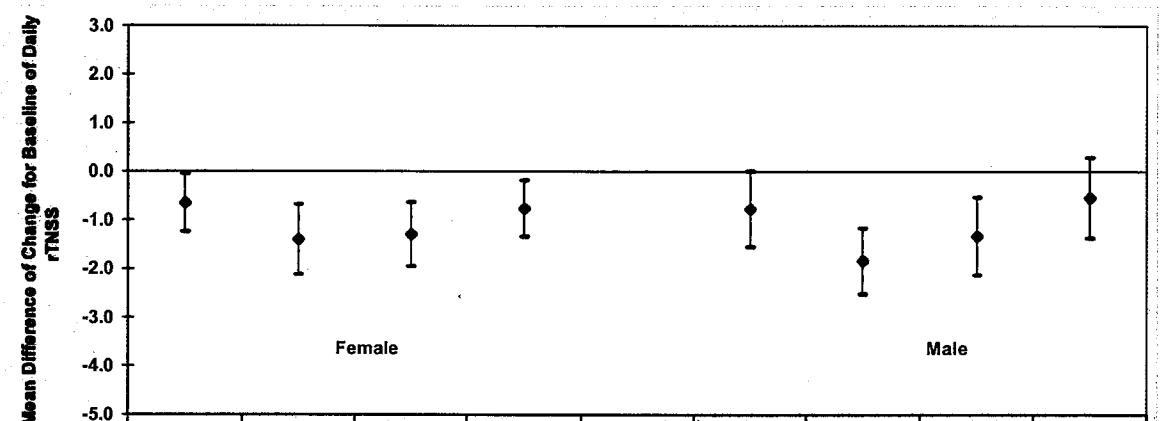
| | ***SAR01 (n=255)*** | ***SAR02 (n=303)*** | ***SAR03 (n=285)*** | ***SAR04 (n=299)*** | ***SAR05 (n=381)*** |
|---|---|---|---|---|---|
| ***Hour*** | **LS Mean Diff. p-value[1]** | **LS Mean Diff. p-value** | **LS Mean Diff. p-value** | **LS Mean Diff. p-value** | **LS Mean Diff. p-value** |
| **Hour 1** | - | - | - | - | -0.09, *p*=0.70 |
| **Hour 2** | - | - | - | - | -0.04, *p*=0.89 |
| **Hour 3** | - | - | - | - | -0.15, *p*=0.56 |
| **Hour 4** | -0.59, *p*=0.060 | -0.08, *p*=0.784 | -0.52, *p*=0.077 | -0.06, *p*=0.844 | -0.21, *p*=0.43 |
| **Hour 5** | - | - | - | - | -0.24, *p*=0.39 |
| **Hour 6** | - | -0.16, *p*=0.592 | -0.23, *p*=0.456 | -0.28, *p*=0.355 | -0.37, *p*=0.19 |
| **Hour 7** | - | - | - | - | -0.05, *p*=0.85 |
| **Hour 8** | -0.71, *p*=0.031 | -0.06, *p*=0.855 | -0.51, *p*=0.118 | -0.75, *p*=0.018 | -0.09, *p*=0.76 |
| **Hour 9** | - | - | - | - | -0.17, *p*=0.56 |
| **Hour 10** | - | -0.16, *p*=0.613 | -0.60, *p*=0.078 | -0.83, *p*=0.009 | -0.25, *p*=0.40 |
| **Hour 11** | - | - | - | - | -0.14, *p*=0.63 |
| **Hour 12** | -1.11, *p*=0.002 | -0.41, *p*=0.216 | -0.67, *p*=0.063 | -0.55, *p*=0.099 | -0.22, *p*=0.46 |
| **Hour 24** | -1.27, *p*<0.001 | -0.53, *p*=0.045 | -1.24, *p*<0.001 | -0.75, *p*=0.006 | - |
| **Day 2** | -1.41, *p*<0.001 | -0.70, *p*=0.016 | -1.63, *p*<0.001 | -0.94, *p*=0.002 | - |
| **Day 3** | -1.37, *p*<0.001 | -0.44, *p*=0.162 | -1.82, *p*<0.001 | -1.17, *p*<0.001 | - |
| **Day 4** | -1.69, *p*<0.001 | -0.73, *p*=0.018 | -1.96, *p*<0.001 | -1.35, *p*<0.001 | - |
| **Day 5** | -1.84, *p*<0.001 | -0.56, *p*=0.061 | -1.95, *p*<0.001 | -1.11, *p*<0.001 | - |

1. p-value is from comparison of treatment groups using ANCOVA at each time point with covariate adjustment for age, gender, center, treatment, and baseline. Baseline is the Hour 0 assessment. 2. The highlight indicated the first significant time-point and confirmed time-point.

***Subgroup Analyses –***

Figure 2, Figure 3, and Figure 4 show the results of the usual subgroup analysis for SAR and PAR studies. The results by gender were highly consistent. There were too few patients to examine results for patients 65 and older. Statistically significant results are not expected in all subgroups due to the reduced sample size and natural variation expected when conducting multiple analyses.

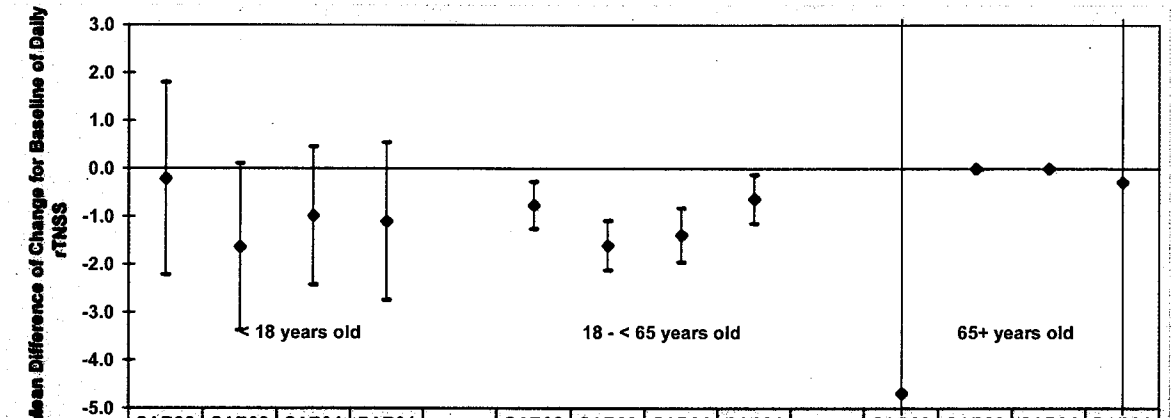
Figure 2. LS Mean and 95% CI of Change from Baseline of Daily rTNSS for Gender Group




| | SAR02 (n=191) | SAR03 (n=151) | SAR04 (n=180) | PAR01 (n=189) | | SAR02 (n=111) | SAR03 (n=132) | SAR04 (n=119) | PAR01 (n=113) |
|---|---|---|---|---|---|---|---|---|---|
| - 95%-LL | -1.24 | -2.12 | -1.96 | -1.33 | | -1.55 | -2.51 | -2.13 | -1.37 |
| - 95%-UL | -0.05 | -0.67 | -0.63 | -0.18 | | 0.01 | -1.16 | -0.53 | 0.29 |
| ◆ FF100 - PL | -0.65 | -1.40 | -1.30 | -0.76 | | -0.77 | -1.84 | -1.33 | -0.54 |

Sub-Groups (n=Patient Counts)

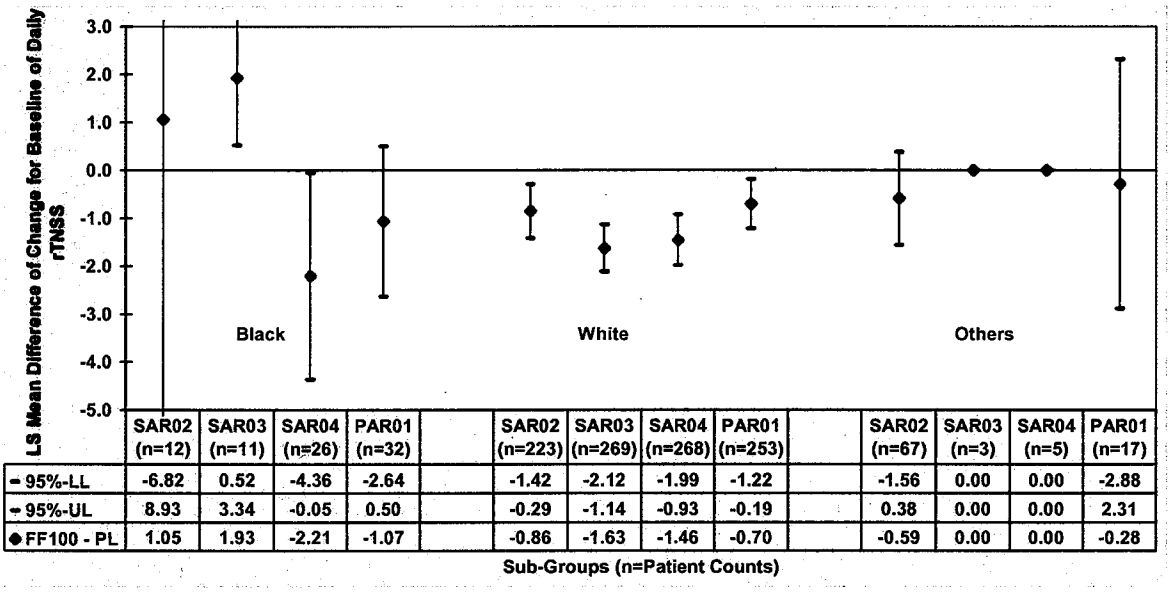
Figure 3. LS Mean and 95% CI of Change from Baseline of Daily rTNSS for Age Group




| | SAR02 (n=27) | SAR03 (n=25) | SAR04 (n=49) | PAR01 (n=32) | | SAR02 (n=265) | SAR03 (n=256) | SAR04 (n=247) | PAR01 (n=260) | | SAR02 (n=10) | SAR03 (n=2) | SAR04 (n=3) | PAR01 (n=10) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95%-LL | -2.22 | -3.38 | -2.43 | -2.75 | | -1.26 | -2.12 | -1.95 | -1.14 | | -17.92 | 0.00 | 0.00 | -5.15 |
| - 95%-UL | 1.79 | 0.10 | 0.45 | 0.54 | | -0.27 | -1.09 | -0.83 | -0.13 | | 8.55 | 0.00 | 0.00 | 4.59 |
| ◆ FF100 - PL | -0.21 | -1.64 | -0.99 | -1.10 | | -0.77 | -1.60 | -1.39 | -0.63 | | -4.68 | 0.00 | 0.00 | -0.28 |

Sub-Groups (n=Patient Counts)

Figure 4. LS Mean and 95% CI of Change from Baseline of Daily rTNSS for Race Group




| | SAR02 (n=12) | SAR03 (n=11) | SAR04 (n=26) | PAR01 (n=32) | | SAR02 (n=223) | SAR03 (n=269) | SAR04 (n=268) | PAR01 (n=253) | | SAR02 (n=67) | SAR03 (n=3) | SAR04 (n=5) | PAR01 (n=17) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95%-LL | -6.82 | 0.52 | -4.36 | -2.64 | | -1.42 | -2.12 | -1.99 | -1.22 | | -1.56 | 0.00 | 0.00 | -2.88 |
| - 95%-UL | 8.93 | 3.34 | -0.05 | 0.50 | | -0.29 | -1.14 | -0.93 | -0.19 | | 0.38 | 0.00 | 0.00 | 2.31 |
| ◆ FF100 - PL | 1.05 | 1.93 | -2.21 | -1.07 | | -0.86 | -1.63 | -1.46 | -0.70 | | -0.59 | 0.00 | 0.00 | -0.28 |

Sub-Groups (n=Patient Counts)

# 2. INTRODUCTION

## 2.1 Overview

Fluticasone Furoate is a new corticosteroid developed by GlaxoSmithKline (GSK), presented as an aqueous suspension in a novel side-actuated nasal spray device for the once daily treatment for symptoms of allergic rhinitis.

The sponsor submitted this application on June 28, 2006 (NDA 22-051) in support of usage of Fluticasone Furoate Nasal Spray ——— the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children 2 years and older.

The sponsor proposed the following statements be added to the clinical studies section for the package insert: (p12, drafet-package-insert-pdf-file.pdf, highlighting added)

"*14.1 Seasonal and Perennial Allergic Rhinitis - Adult and Adolescent Patients Aged 12 Years and Older:*

1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

**The sponsor's submission included** twelve studies outlined in Table 4. Eight of them are adult and adolescent studies and the remaining four are pediatric studies. This reviewer will focus on efficacy studies: SAR01-SAR05, PAR01, PED01, and PED02. Henceforth, the studies are referred to by number as SAR, PAR or PED studies as shown in the table below.

Table 4. Clinical Trials

| *Study* | *Type* | *Population* | *Duration* | *Dose* | *N* |
|---|---|---|---|---|---|
| **Adult and Adolescent Studies** | | | | | |
| **FFR20001** (SAR01) | **Phase II –** SAR/Dose-ranging (US, Mountain Cedar Season) | 12 yrs and older | 2 weeks | FF50mcg QD<br>FF100mcg QD<br>FF200mcg QD<br>FF400mcg QD<br>Placebo | 127<br>127<br>129<br>130<br>128 |
| **FFR30003** (SAR02) | Phase III - SAR (US, Mountain Cedar Season) | 12 yrs and older | 2 weeks | FF100mcg QD<br>Placebo | 152<br>151 |
| **FFR103184** (SAR03) | Phase III - SAR (Europe, Grass Season) | 12 yrs and older | 2 weeks | FF100mcg QD<br>Placebo | 141<br>144 |
| **FFR104861** (SAR04) | **Phase III – SAR** (US, Ragweed Season) | 12 yrs and older | 2 weeks | FF100mcg QD<br>Placebo | 151<br>148 |
| **FFR30002** (PAR01) | **Phase III – PAR** (US/Canada) | 12 yrs and older | 4 weeks | FF100mcg QD<br>Placebo | 149<br>153 |
| **FFR102123** (PAR02) | **Phase III – PAR/Long term** safety (Europe, South America, Australasia) | 12 yrs and older | 52 weeks | FF100mcg QD<br>Placebo | 605<br>201 |
| **FFR20002** (PAR03) | Phase III - PAR/HPA axis safety (US/Canada) | 12 yrs and older | 6 weeks | FF100mcg QD<br>Placebo<br>Placebo/Prednisone | 48<br>51<br>13 |
| **FFR101816** (SAR05) | **Phase III – ACC** (US, Ragweed Pollen) | 12 yrs and older | One day | FF100mcg QD<br>Placebo | 191<br>191 |
| **Pediatric Studies** | | | | | |
| **FFR100010** (PED01) | **Phase III – SAR** (US, Grass and Ragweed Seasons) | 2 to < 12 yrs old | 2 weeks | FF50mcg QD<br>FF100mcg QD<br>Placebo | 184<br>184<br>186 |
| **FFR30008** (PED02) | **Phase III – PAR** (North America, South America, Europe) | 2 to < 12 yrs | 12 weeks | FF50mcg QD<br>FF100mcg QD<br>Placebo | 185<br>185<br>188 |
| **FFR100012** (PED03) | **Phase III – HPA axis safety** (US) | 18 to 60 yrs | 6 weeks | FF100mcg QD<br>Placebo | 57<br>55 |
| **FFR101747** (PED04) | **Phase III – SAR/PAR** Knemometry safety (Denmark) | 18 to 60 yrs | 2 weeks | FF100mcg QD<br>Placebo | 58 (Crossover design) |

## 2.2 Data Sources

Documents reviewed can be found in: \\Cdsesub1\N22051\N_000

# 3. STATISTICAL EVALUATION

## 3.1 Evaluation of Efficacy

The evaluation of efficacy will include three parts: 1.) Dose-finding and pivotal efficacy studies; 2.) Allergen Challenge Chamber Study; 3.) Pediatric studies.

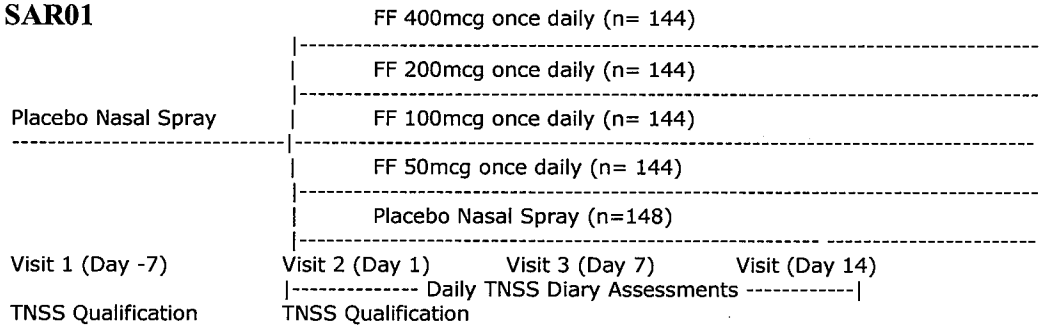
### *3.1.1 Dose-finding (SAR01) and Pivotal Efficacy Studies (SAR02, 03, 04, PAR01)*

#### 3.1.1.1 Design

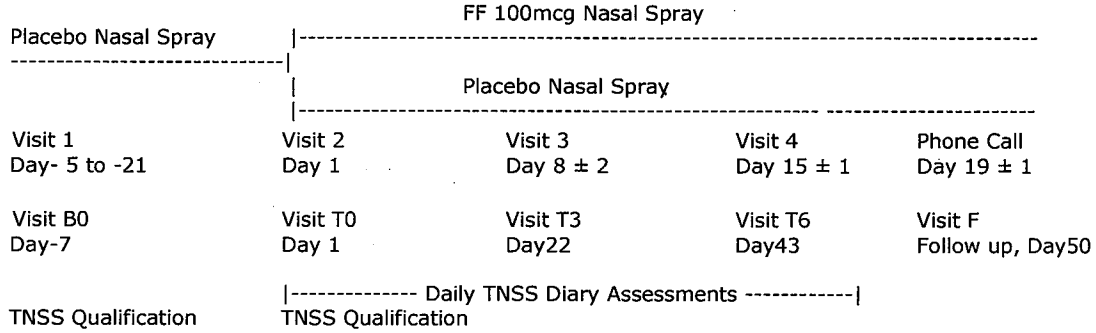
The objective of the dose-finding (SAR01) study was to find the minimum effective dose of Fluticasone Furoate Nasal Spray once daily in the treatment of patients 12 years and older with SAR. This study was designed as a phase II, double-blind, randomized, placebo-controlled, multi-center, dose-ranging study to evaluate the effects and safety of FF 50, 100, 200, and 400mcg doses once daily in patients 12 years and older with SAR.

The objective of the four phase III studies (SAR02, 03, 04, and PAR01) was to evaluate the effectiveness and safety of FF100mcg once daily in the treatment of adult and adolescent patients 12 years and older with SAR or PAR. All four studies were double-blind, randomized, multi-center, placebo-controlled, parallel-group trials with one-week, single-blind, placebo run-in periods followed by either a 2-week (SAR studies) or a 4-week (PAR study) double-blind treatment period. (See the study flow charts below.)

**Study SAR01**




**SAR and PAR Studies**



The patients in these five studies had at least a two-year history of SAR or PAR and a positive skin test to the local spring pollen. The main inclusion criteria were:

- **Males or eligible females aged** ≥ 12 years at Visit 2 (at least 10% of the subjects were to be between the ages of 12 and 17, inclusive, at randomization).
- **Diagnosis of SAR, defined as: clinical history** of SAR with seasonal onset and offset of nasal allergy symptoms during each of the last two allergy seasons (specifically mountain cedar for SAR01 and SAR02, grass for SAR03 or fall/ragweed for SAR04), and a positive skin test (by prick method) to the allergen within 12 months prior to Visit 1 or at Visit 1 (Visit 1 only for SAR01).

In vitro tests for specific IgE were not allowed as a diagnosis of SAR, except in SAR03 where historical tests were allowed if conducted less than 12 months prior to Visit 1. Subjects who met the above criteria and who may have also had PAR or vasomotor rhinitis (PAR only in SAR01) were still eligible for randomization.

### 3.1.1.2 Patient Disposition

**Table 5 summarizes the patient's disposition for** the dose-finding study SAR01. A total of 642 subjects who satisfied the inclusion and exclusion criteria were randomly assigned to receive FF 400, 200, 100, 50mcg, and Placebo in Study SAR01. Six hundred and twenty subjects (96.6%) completed the study. The percent of discontinuation was similar in the treatment groups. Only one patient (FF100), who withdrew without taking randomized treatment, was excluded from the ITT analysis set.

**Table 5. Patients' Accountability N (%), Dose-finding Study SAR01**

| | SAR01 (n=642) | | | | |
|---|---|---|---|---|---|
| | ***Placebo*** | ***FF50mcg*** | ***FF100mcg*** | ***FF200mcg*** | ***FF400mcg*** |
| Entered | 128 | 127 | 128 | 129 | 130 |
| Completed | 124 (96.9) | 121 (95.3) | 125 (97.7) | 124 (96.1) | 126 (96.9) |
| Discontinued | 4 (3.1) | 6 (4.7) | 3 (2.3) | 5 (3.9) | 4 (3.1) |
| ***Reason of early discontinuation*** | | | | | |
| Adverse Event | 1 | 2 | 1 | 4 | 1 |
| Non-Compliance/disqualify | 0 | 1 | 0 | 0 | 1 |
| Lack of Efficacy | 0 | 0 | 0 | 1 | 0 |
| Pt. Withdraw Consent | 0 | 1 | 1 | 0 | 1 |
| Lost Follow-up | 0 | 2 | 0 | 0 | 1 |
| Others | 3 | 0 | 1 | 0 | 0 |
| ***Analysis Population*** | | | | | |
| ITT | 128 | 127 | 127 | 129 | 130 |

Data: Dispos.xpt; Code: Demog.sas.

Table 6, on the following page, summarizes the **patient's disposition for three SAR (SAR02, 03,** and 04) studies and one PAR (PAR01) study. A total of 887 subjects who met the criteria were randomly assigned to receive FF100mcg or placebo in SAR studies. Eight hundred and thirty five subjects (94%) completed the study. The percent of subjects discontinuing due to the lack of efficacy was slightly higher in placebo group compared to FF100mcg group.

A total of 302 subjects who met the criteria were randomly assigned to receive FF100mcg or placebo in study PAR01. Two hundred and seventy nine subjects (92%) completed the study. The percent of subjects discontinuing was similar between the two treatment groups.

**Table 6. Patients' Accountability N (%), SAR02, 03, and 04 Pooled and PAR01**

| | ***Pooled SAR (n=887)*** | | ***PAR (n=302)*** | |
|---|---|---|---|---|
| | ***Placebo*** | ***FF100mcg*** | ***Placebo*** | ***FF100mcg*** |
| Entered | 443 | 444 | 152 | 150 |
| Completed | 408 (92.1) | 427 (96.2) | 141 (92.8) | 138 (92) |
| Discontinued | 35 (7.9) | 17 (3.8) | 11 (7.2) | 12 (8) |
| ***Reason of early discontinuation*** | | | | |
| Adverse Event | 6 | 0 | 4 | 4 |
| Non-Compliance/disqualify | 6 | 2 | 3 | 1 |
| Lack of Efficacy | 13 | 4 | 1 | 3 |
| Pt. Withdraw Consent | 6 | 6 | 1 | 3 |
| Lost Follow-up | 0 | 1 | 0 | 0 |
| Others | 4 | 4 | 2 | 1 |
| ***Analysis Population*** | | | | |
| PP | 423 | 436 | 139 | 133 |
| ITT | 443 | 444 | 152 | 150 |

Data: Dispos.xpt; Code: Demog.sas.

### 3.1.1.3 Demographic and Baseline Characteristic

The demographics and baseline characteristics for all randomized patients for the dose-finding study SAR01 are summarized in Table 7. The majority of the subjects were Caucasian (60%), American Hispanic (35%), and female (66%) with median age of 40. The demographic and baseline characteristics were balanced except there were only 5% or fewer subjects aged from 12 to 17 years old in FF100mcg and FF200mcg treatment groups. The baseline value of daily rTNSS and AM pre-dose iTNSS were similar across treatment groups.

Table 7. **ITT Subjects' Demographics and Baseline** Characteristics, Dose-finding Study SAR01

| | ***SAR01 (n=641)*** | | | | |
|---|---|---|---|---|---|
| | ***Placebo (n=128)*** | ***FF50mcg (n=127)*** | ***FF100mcg (n=127)*** | ***FF200mcg (n=129)*** | ***FF400mcg (n=130)*** |
| ***Sex*** | | | | | |
| Female | 85 (66%) | 81 (64%) | 86 (68%) | 83 (64%) | 86 (66%) |
| Male | 43 (34%) | 46 (36%) | 41 (32%) | 46 (36%) | 44 (34%) |
| ***Race*** | | | | | |
| White | 76 (59%) | 73 (57%) | 75 (59%) | 76 (59%) | 79 (61%) |
| Black | 6 | 9 | 4 | 3 | 3 |
| American Hispanic | 46 (36%) | 42 (33%) | 47 (37%) | 49 (38%) | 48 (37%) |
| Others | 0 | 3 | 1 | 1 | 0 |
| ***Age*** | | | | | |
| **12 - 17** | **11 (9%)** | **10 (8%)** | **6 (5%)** | **5 (4%)** | **11 (8%)** |
| **18 - 64** | **112 (88%)** | **111 (87%)** | **116 (91%)** | **121 (94%)** | **115 (88%)** |
| 65+ | 5 (4%) | 6 (5%) | 5 (4%) | 3 (2%) | 4 (3%) |
| Mean (SD) | 38.6 (14.0) | 38.3 (14.5) | 40.6 (13.6) | 39.4 (13.1) | 39.6 (13.9) |
| Median | 39 | 37 | 42 | 39 | 40.5 |
| **Range** | **12 - 75** | **12 - 80** | **13 - 70** | **12 - 71** | **13 - 71** |

| | | | | | |
|---|---|---|---|---|---|
| ***Duration of SAR (yrs)*** | | | | | |
| 2 - < 5 | 6 (5%) | 10 (8%) | 10 (8%) | 18 (6%) | 13 (10%) |
| 5 - < 10 | 30 (23%) | 34 (27%) | 28 (22%) | 26 (20%) | 32 (25%) |
| >= 10 | 92 (72%) | 83 (65%) | 89 (70%) | 95 (74%) | 85 (65%) |
| ***Daily rTNSS*** | | | | | |
| Mean (SD) | 9.6 (1.6) | 9.6 (1.5) | 9.5 (1.4) | 9.5 (1.6) | 9.6 (1.7) |
| Median | 9.56 | 9.75 | 9.37 | 9.62 | 9.75 |
| **Range** | **6 - 12** | **5 - 12** | **4 - 12** | **5 - 12** | **5 - 12** |
| ***AM Pre-dose iTNSS*** | | | | | |
| Mean (SD) | 9.2 (1.8) | 9.1 (1.7) | 9.3 (1.6) | 9.2 (1.8) | 9.1 (1.8) |
| Median | 9.2 | 9.0 | 9.5 | 9.5 | 9.0 |
| **Range** | **5.2 - 12** | **5.5 - 12** | **5.5 - 12** | **5.2 - 12** | **5.5 - 12** |

Data: DE.xpt; AT.xpt; RE.xpt; IN.xpt; Code: Demog.sas

The demographics and baseline characteristics for all randomized patients for Study SAR02, SAR03, SAR04, and PAR01 are summarized in Table 8. The majority of the subjects were Caucasian (73%, 95%, 90%, and 82%, respectively). The demographic and baseline characteristics were balanced across treatment groups except that the subjects in Study SAR03 were younger (median age was 28.5) compared to the subjects in other studies (median age were ranged from 34.5 to 38) and had milder symptoms at the baseline (rTNSS was 8.3) compared to other SAR studies (rTNSS ranged from 9.6 to 9.9).

Table **8. ITT Subjects' Demographics and Baseline Characteristics**

| | ***SAR02 (n=303)*** | | ***SAR03 (n=285)*** | |
|---|---|---|---|---|
| | ***Placebo (n=151)*** | ***FF100mcg (n=152)*** | ***Placebo (n=144)*** | ***FF100mcg (n=141)*** |
| ***Sex*** | | | | |
| Female | 100 (66.2) | 92 (60.5) | 80 (55.6) | 71 (50.4) |
| Male | 51 (33.8) | 60 (39.5) | 64 (44.4) | 70 (49.7) |
| ***Race*** | | | | |
| White | 113 (74.8) | 110 (72.4) | 136 (94.4) | 135 (95.7) |
| Black | 6 (4.0) | 6 (4.0) | 7 (4.9) | 4 (2.8) |
| Others | 31 (20.5) | 36 (23.7) | 1 (0.7) | 2 (1.4) |
| ***Age*** | | | | |
| **12 - 17** | **11 (7.3)** | **16 (10.5)** | **11 (7.6)** | **14 (9.9)** |
| **18 - 64** | **132 (87.4)** | **133 (87.5)** | **132 (91.7)** | **126 (89.4)** |
| 65+ | 7 (4.6) | 3 (2.0) | 1 (0.7) | 1 (0.7) |
| Mean (SD) | 38.1 (13.6) | 37.0 (13.9) | 29.4 (10.9) | 30.7 (11.7) |
| Median | 38 | 37 | 28 | 29 |
| **Range** | **13 - 67** | **12 - 75** | **12 - 65** | **12 - 65** |
| ***Duration of SAR (yrs)*** | | | | |
| 2 - < 5 | 16 (10.7) | 24 (15.8) | 32 (22.2) | 36 (25.5) |
| 5 - < 10 | 37 (24.7) | 32 (21.1) | 50 (34.7) | 38 (27.0) |
| >= 10 | 97 (64.7) | 96 (63.2) | 62 (43.1) | 67 (47.5) |
| ***Daily rTNSS*** | | | | |
| Mean (SD) | 9.7 (1.3) | 9.8 (1.8) | 8.4 (1.4) | 8.3 (1.5) |
| Median | 9.9 | 9.9 | 8.3 | 8.3 |
| **N, Range** | **150, 6.8 - 12** | **152, 6.6 - 12** | **143, 5.9 - 11.9** | **140, 5.6 - 12** |
| ***AM Pre-dose iTNSS*** | | | | |
| Mean (SD) | 9.5 (1.5) | 9.4 (1.6) | 8.3 (1.7) | 8.1 (1.7) |
| Median | 9.8 | 9.3 | 8.0 | 8.3 |
| **N, Range** | **150, 5.8 - 12** | **152, 5.5 - 12** | **143, 4.5 - 12** | **140, 4.8 - 12** |
| | ***SAR04 (n=299)*** | | ***PAR (n=302)*** | |
| | ***Placebo (n=148)*** | ***FF100mcg (n=151)*** | ***Placebo (n=152)*** | ***FF100mcg (n=150)*** |

| | | | | |
|---|---|---|---|---|
| ***Sex*** | | | | |
| Female | 84 (56.8) | 96 (63.6) | 84 (55.3) | 105 (70.0) |
| Male | 64 (43.2) | 55 (36.4) | 68 (44.7) | 45 (30.0) |
| ***Race*** | | | | |
| White | 129 (87.2) | 139 (92.1) | 125 (82.2) | 128 (82.3) |
| Black | 16 (10.8) | 10 (6.6) | 18 (11.8) | 14 (9.3) |
| Others | 3 (2.0) | 2 (1.3) | 9 (5.9) | 8 (5.3) |
| ***Age*** | | | | |
| **12 - 17** | **27 (18.2)** | **22 (14.6)** | **20 (13.2)** | **12 (8.0)** |
| **18 - 64** | **119 (80.4)** | **128 (84.8)** | **130 (85.5)** | **130 (86.7)** |
| 65+ | 2 (1.4) | 1 (0.7) | 2 (1.3) | 8 (5.3) |
| Mean (SD) | 34.5 (14.1) | 35.4 (13.8) | 35.7 (14.8) | 37.8 (14.9) |
| Median | 35 | 36 | 35 | 37 |
| **Range** | **12 - 74** | **12 - 70** | **12 - 74** | **13 - 76** |
| ***Duration of SAR (y)*** | | | | |
| 2 - < 5 | 19 (12.8) | 15 (9.9) | 33 (21.7) | 26 (17.3) |
| 5 - < 10 | 29 (19.6) | 25 (16.6) | 47 (30.9) | 35 (23.3) |
| >= 10 | 100 (67.6) | 111 (73.5) | 72 (47.4) | 89 (59.3) |
| ***Daily rTNSS*** | | | | |
| Mean (SD) | 9.9 (1.3) | 9.6 (1.6) | 8.7 (1.7) | 8.6 (1.6) |
| Median | 9.9 | 9.6 | 8.6 | 8.6 |
| **N, Range** | **148, 6.5 - 12** | **151, 4 - 12** | **152, 6 - 12** | **150, 5.3 - 12** |
| ***AM Pre-dose iTNSS*** | | | | |
| Mean (SD) | 9.3 (1.6) | 9.4 (1.6) | 8.2 (2.1) | 8.3 (2.2) |
| Median | 9.4 | 9.5 | 8.1 | 8.3 |
| **N, Range** | **148, 4.8 - 12** | **151, 5.8 - 12** | **152, 3 - 12** | **150, 2.8 - 12** |

Data: DE.xpt; AT.xpt; RE.xpt; IN.xpt; Code: Demog.sas

#### 3.1.1.4 Statistical Methodologies

Primary Efficacy Endpoint

Primary Efficacy Endpoint was the mean change from baseline over the entire treatment period in Daily rTNSS which was defined as the average of reflective AM TNSS and PM TNSS (the maximum value was 12). Total Nasal Symptom Score (TNSS) was comprised of individual symptom scores for runny nose, sneezing, itchy nose, and nasal congestion based on symptoms experienced over the previous 12 hours and was performed in the AM (AM rTNSS) and PM (PM rTNSS). Each symptom was scored on a 4-point scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms).

Key Secondary Endpoints

- **Mean change from baseline over the en**tire treatment period in AM Pre-dose iTNSS which was defined as sum of the 4 individual nasal symptom score assessments for rhinorrhea, nasal congestion, nasal itching, and sneezing experienced at the moment immediately prior to taking their dose in which each symptom was scored on a scale of 0 to 3.
- **Mean change from baseline over the entire treatment period in the Daily rTOSS (except** for PAR study). The Total Ocular Symptoms Score (TOSS) was the sum of 3 individual symptom scores for itching/ burning eyes, tearing/watering eyes, and eye redness in which each symptom was scored on a scale of 0 to 3. The rTOSS was a rating of the severity of symptoms over the previous 12 hours and was experienced in the AM (AM rTOSS) and PM (PM rTOSS).

The Daily rTOSS was the average of the AM rTOSS and PM rTOSS assessments.

- **Overall evaluation of response to therapy,** which was based on a 7-point categorical scale in which the subjects rate their perception of the change or lack of change in their allergic symptoms at the end of the study. The 7 categories were: significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, and significantly worse.

- **Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The RQLQ was** administered at Visit 2 (Randomization) and Visit 4 (End of Study)/Early Withdrawal and scored **according to the instrument developers' guidelines [Juniper,** 1991]. The RQLQ consists of 28 items scored on a 10-point (0 to 9) categorical scale. These 28 items constitute 7 domains as follows:
    - **Activities (3 items): 1, 2, 3**
    - **Sleep (3 items): 4, 5, 6**
    - **Non-Hayfever Symptoms (7 items): 7, 8, 9, 10, 11, 12, 13**
    - **Practical Problems (3 items): 14, 15, 16**
    - **Nasal Symptoms (4 items): 17, 18, 19, 20**
    - **Eye Symptoms (4 items): 21, 22, 23, 24**
    - **Emotional (4 items): 25, 26, 27, 28**

At any time point, mean scores for each individual domain was calculated for each subject by averaging the item scores included within that domain. The global score at any time point was calculated for each subject by averaging all item scores.

Analyses of Efficacy

The primary analysis was based on the ITT population, which was defined as all randomized subjects who receive at least one dose of study drug The analysis method was the pairwise comparisons of treatment groups (active vs. placebo) using analysis of covariance (ANCOVA) adjusting for baseline rTNSS, investigative site or country (SAR03), age, and gender.

Overall response to therapy was analyzed using the logistic regression to test for treatment difference, adjusting for age and sex. The investigational site (or region/country) was also considered as a covariate in the analysis model if the randomization was center-based (or stratified by region/country).

The primary analysis of the RQLQ was the mean change from baseline in the global score compared between the treatment groups at endpoint. Baseline was defined as the Visit 2 questionnaire. Endpoint was defined as the last available on treatment questionnaire. An analysis of covariance model including terms for treatment, investigator, treatment-by-investigator interaction (for studies SAR03 and PAR01 used **country as "investigator"), and baseline was** used to test statistical differences in treatment group mean changes from baseline at endpoint. A mean change from baseline of 0.5 or more for the RQLQ scores was considered the smallest change that subjects perceive as beneficial. In addition, if the difference between treatments in the global score was found to be significant, then individual domain scores between treatment groups were compared.

Multiple Comparisons and Multiplicity
The primary efficacy endpoint served as a gatekeeper for the interpretation of treatment comparisons for the key secondary efficacy and health outcomes endpoints. To control for multiplicity across the key secondary efficacy endpoints and the health outcomes endpoint (i.e., mean change from baseline to endpoint in the global score of the RQLQ), tests of $H_0$ were performed in a sequential manner to control the type I error rate at 0.05 as follows:

1. Mean change from baseline over the entire treatment period in AM pre-dose iTNSS.
2. Overall evaluation of response to therapy.
3. The endpoints of the mean change from baseline over the entire treatment period in daily rTOSS (except for PAR study) and the mean change from baseline to endpoint in the RQLQ global score will be controlled at the 0.05 **significance level using Hochberg's method.**

No multiplicity adjustments were made on the other secondary efficacy endpoints. Any p- values $\leq 0.05$ was identified as nominally significant.

Missing Data Handling
The change from baseline over the entire treatment period in daily rTNSS was calculated for each subject as the average of the non-missing daily rTNSS during the treatment period minus the baseline daily rTNSS.

For RQLQ, each individual domain mean score for any subject at any time point was only calculated if at least 75% of the items in that domain were answered. The global score for any subject at any time point was only calculated if at least 75% of all items are answered. Otherwise, mean scores was set to missing.

In some cases during Visit 4 or the Early Withdrawal visit a subject may not be able to respond to a question concerning one or more of the 3 individualized activities identified at baseline because the activity was not performed since the baseline visit. For these cases the instrument developers had specified a mechanism for pro-rating individualized responses using baseline and post-baseline scores. The pro-rating process was only used for the 3 individualized activities and was applied only after assessing whether a sufficient number of responses (i.e., 75%) were present to calculate individual domain and global scores.

### 3.1.1.5 Sponsor's Results and Conclusions

**The sponsor's results for the p**rimary efficacy endpoint and key secondary endpoints of Study SAR and PAR studies was provided in following table that is proposed for the labeling (labeling.pdf)

*Table 2: Change from Baseline in Efficacy Variables from Studies in Adult and Adolescent Patients with Seasonal Allergic Rhinitis*

| *Study Number*<br>*FFR30003*<br>*FFR103184*<br>*FFR104861*<br>*Endpoint* | *Vehicle Placebo*<br>*(n = 150)*<br>*(n = 144)*<br>*(n = 148)*<br>*Mean Change* | *TRADE NAME 110 mcg /day*<br>*(n =152)*<br>*(n = 141)*<br>*(n = 151)*<br>*Mean Change* | *Difference**<br>*(95% CI)* |
|---|---|---|---|
| *rTNSS (scale 0 to 12)* | | | |
| *FFR30003* | *-2.25* | *-3.03* | *-0.78 (-1.28, -0.27)* |
| *FFR103184* | *-3.18* | *-4.94* | *-1.76 (-2.28, -1.23)* |
| *FFR104861* | *-2.07* | *-3.55* | *-1.47 (-2.01, -0.94)* |
| *iTNSS (scale 0 to 12)* | | | |
| *FFR30003* | *-1.47* | *-2.38* | *-0.90 (-1.38, -0.42)* |
| *FFR103184* | *-2.60* | *-4.50* | *-1.90 (-2.42, -1.38)* |
| *FFR104861* | *-1.53* | *-2.90* | *-1.38 (-1.90, -0.85)* |
| *rTOSS (scale 0 to 9)* | | | |
| *FFR30003* | *-1.60* | *-2.15* | *-0.55 (-0.95, -0.14)* |
| *FFR103184* | *-2.26* | *-3.00* | *-0.74 (-1.14, -0.34)* |
| *FFR104861* | *-1.63* | *-2.23* | *-0.60 (-1.01, -0.19)* |
| *RQLQ (scale 0 to 6)* | | | |
| *FFR30003* | *-0.97* | *-1.66* | *-0.69 (-1.08, -0.30)* |
| *FFR103184* | *-1.64* | *-2.21* | *-0.57 (-0.86, -0.28)* |
| *FFR104861* | *-1.16* | *-1.78* | *-0.60 (-0.93, -0.27)* |

* *$p<0.01$ for all differences*
*rTNSS = reflective total nasal symptoms score*
*iTNSS = instantaneous total nasal symptoms score*
*rTOSS = reflective total ocular symptoms score*
*RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire*

*Table 3: Change from Baseline in Efficacy Variables from Study in Adult and Adolescent Patients with Perennial Allergic Rhinitis*

| *Endpoint* | *Vehicle Placebo (n = 153) Mean Change* | *TRADE NAME 110 mcg Once Daily (n = 149) Mean Change* | *Difference** *(95% CI)* |
|---|---|---|---|
| *rTNSS (scale 0 to 12)* | *-2.08* | *-2.78* | *-0.71 (-1.20, -0.21)* |
| *iTNSS (scale 0 to 12)* | *-1.75* | *-2.45* | *-0.71 (-1.20, -0.21)* |
| *RQLQ (scale 0 to 6)* | *-1.18* | *-1.40* | *-0.23 (-0.59, 0.13)* |

* *$p = 0.005$ for rTNSS, 0.006 for iTNSS, and 0.214 for RQLQ*
*rTNSS = reflective total nasal symptoms score*
*iTNSS = instantaneous total nasal symptoms score*
*RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire"*

### 3.1.1.6 Reviewer's Efficacy Analysis

***Minimum Effective Dose for SAR –***
For Study SAR01, the dose-finding study, this reviewer confirmed the results of the sponsor's primary analyses. Table 9 shows the primary efficacy results for the ITT population. FF50mcg is shown to be the minimum effective dose for SAR. The dose FF100mcg was chosen for the phase III studies.

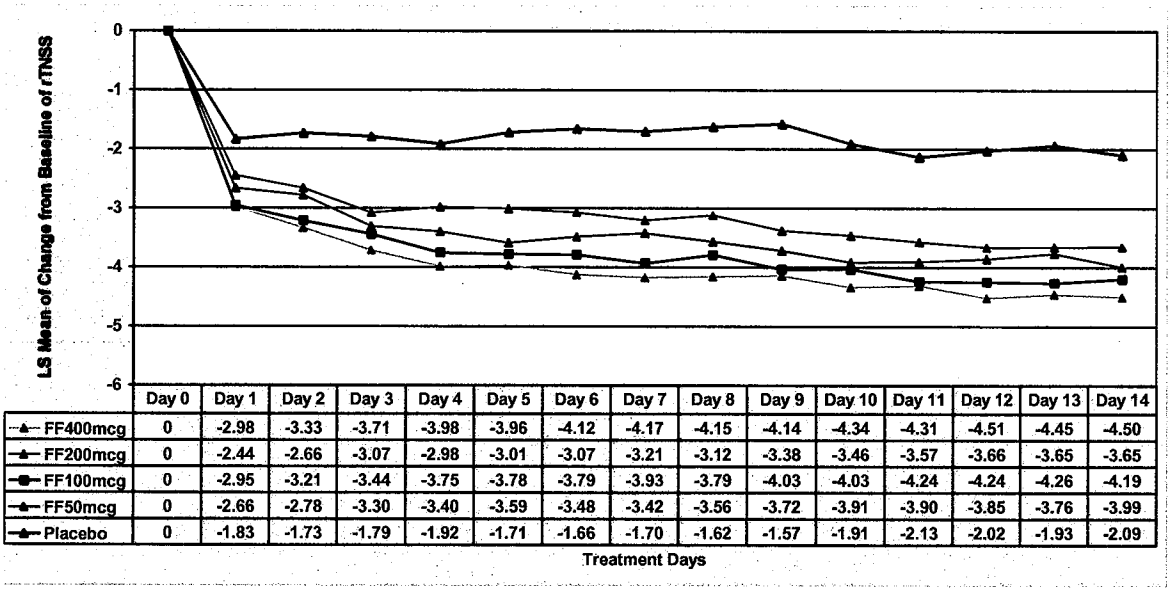
Table 9. Change from Baseline in Daily rTNSS Averaged over 2 Weeks

| Treatment | Baseline Mean (SD) | Change from Baseline | | Treatment Comparison FF vs. Placebo | | |
|---|---|---|---|---|---|---|
| | | N | LS Mean (SE) | LS Mean Difference (SE) | 95% CI | p-value [a] |
| ***Daily rTNSS (Day 1-14) SAR01 For ITT Population*** | | | | | | |
| FF 400mcg | 9.58 (1.71) | 130 | -4.02 (0.21) | -2.19 (0.28) | (-2.75, -1.62) | <0.001 |
| FF 200mcg | 9.49 (1.57) | 129 | -3.19 (0.21) | -1.36 (0.29) | (-1.93, -0.79) | <0.001 |
| FF 100mcg | 9.48 (1.42) | 127 | -3.84 (0.21) | -2.01 (0.29) | (-2.58, -1.44) | <0.001 |
| FF 50mcg | 9.57 (1.49) | 127 | -3.51 (0.21) | -1.68 (0.29) | (-2.24, -1.10) | <0.001 |
| Placebo | 9.57 (1.64) | 128 | -1.82 (0.21) | - | - | - |

a: a: p-value is from a repeated measures ANCOVA with treatment, baseline, gender, age, and center.

Figure 5 shows LS Mean Change from Baseline of daily rTNSS over the treatment period. The largest improvement in symptoms is seen at Day 1. The effect size increases during the rest of the treatment period.

Figure 5. LS Mean Change from Baseline of Daily rTNSS




| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FF400mcg | 0 | -2.98 | -3.33 | -3.71 | -3.98 | -3.96 | -4.12 | -4.17 | -4.15 | -4.14 | -4.34 | -4.31 | -4.51 | -4.45 | -4.50 |
| FF200mcg | 0 | -2.44 | -2.66 | -3.07 | -2.98 | -3.01 | -3.07 | -3.21 | -3.12 | -3.38 | -3.46 | -3.57 | -3.66 | -3.65 | -3.65 |
| FF100mcg | 0 | -2.95 | -3.21 | -3.44 | -3.75 | -3.78 | -3.79 | -3.93 | -3.79 | -4.03 | -4.03 | -4.24 | -4.24 | -4.26 | -4.19 |
| FF50mcg | 0 | -2.66 | -2.78 | -3.30 | -3.40 | -3.59 | -3.48 | -3.42 | -3.56 | -3.72 | -3.91 | -3.90 | -3.85 | -3.76 | -3.99 |
| Placebo | 0 | -1.83 | -1.73 | -1.79 | -1.92 | -1.71 | -1.66 | -1.70 | -1.62 | -1.57 | -1.91 | -2.13 | -2.02 | -1.93 | -2.09 |

***Primary Efficacy for SAR and PAR –***

The primary efficacy endpoint for the SAR and PAR studies was the mean change from baseline over the entire treatment period (2 weeks for SAR studies and 4 weeks for PAR study) in daily rTNSS. **This review confirmed the sponsor's** primary analysis results. (Note: the sponsor's report for study PAR01 used the treatment actually taken by 3 subjects who were miss-assigned to treatment). Table 10 displays the primary efficacy results in the ITT population (using randomized treatment), which shows that subjects treated with FF100mcg once daily exhibited

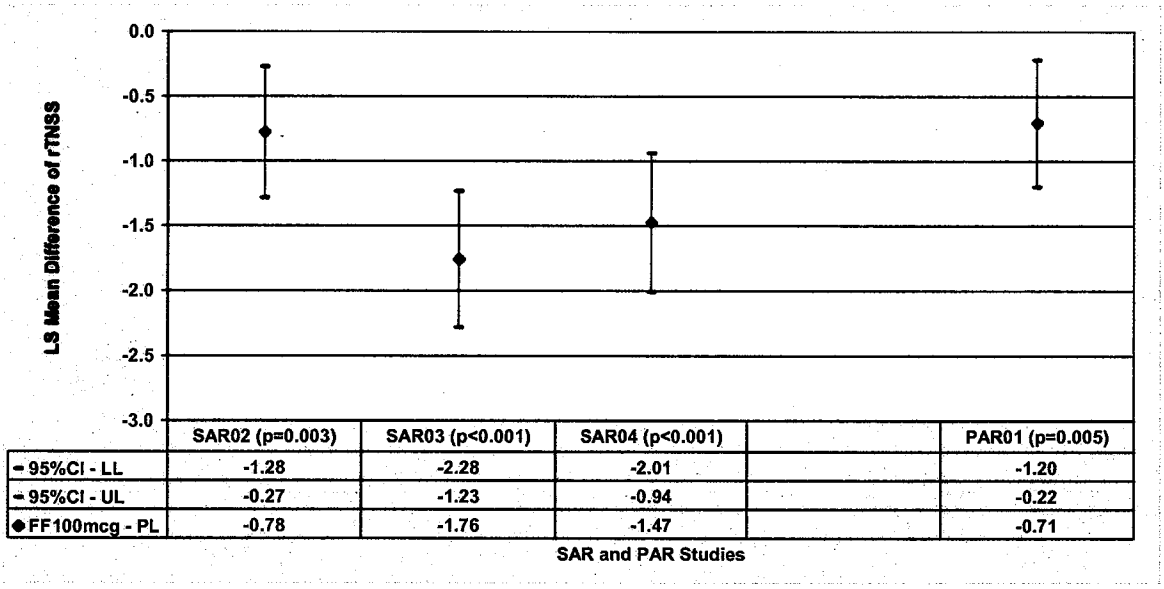
statistically significantly greater decreases in mean daily rTNSS than placebo-treated subjects. Figure 6 shows the magnitude of effect size of SAR and PAR studies.

Table 10. Change from Baseline in Primary Efficacy Variables: Daily rTNSS

| Treatment | Baseline Mean (SD) | Change from Baseline | | Treatment Comparison FF vs. Placebo | | |
|---|---|---|---|---|---|---|
| | | N | LSM (SE) | LSMD (SE) | 95% CI | p-value [a] |
| ***Daily rTNSS (Day 1-14) SAR02 (scale 0 - 12) – ITT*** | | | | | | |
| FF100mcg | 9.85 (1.37) | 152 | -3.03 (0.21) | -0.78 (0.26) | (-1.28, -0.27) | 0.003 |
| Placebo | 9.74 (1.30) | 150 | -2.25 (0.21) | - | - | - |
| ***Daily rTNSS (Day 1-14) SAR03 (scale 0 - 12) – ITT*** | | | | | | |
| FF100mcg | 8.34 (1.47) | 140 | -4.94 (0.20) | -1.76 (0.27) | (-2.28, -1.23) | <0.001 |
| Placebo | 8.38 (1.35) | 143 | -3.18 (0.20) | - | - | - |
| ***Daily rTNSS (Day 1-14) SAR04 (scale 0 - 12) – ITT*** | | | | | | |
| FF100mcg | 9.64 (1.56) | 151 | -3.55 (0.21) | -1.47 (0.27) | (-2.01, -0.94) | <0.001 |
| Placebo | 9.87 (1.34) | 147 | -2.07 (0.22) | - | - | - |
| ***Daily rTNSS (Day 1-42) PAR01 (scale 0 - 12) – ITT*** | | | | | | |
| FF100mcg | 8.63 (1.62) | 150 | -2.78 (0.21) | -0.71 (0.25) | (-1.20, -0.22) | 0.005 |
| Placebo | 8.67 (1.74) | 152 | -2.07 (0.21) | - | - | - |

a: p-value is from a repeated measures ANCOVA with treatment, baseline, gender, age, and center.
LSM=LS Mean; LSMD = LS Mean Difference.

Figure 6. Primary Analysis of Daily rTNSS averaged over 2 Weeks for Four Studies

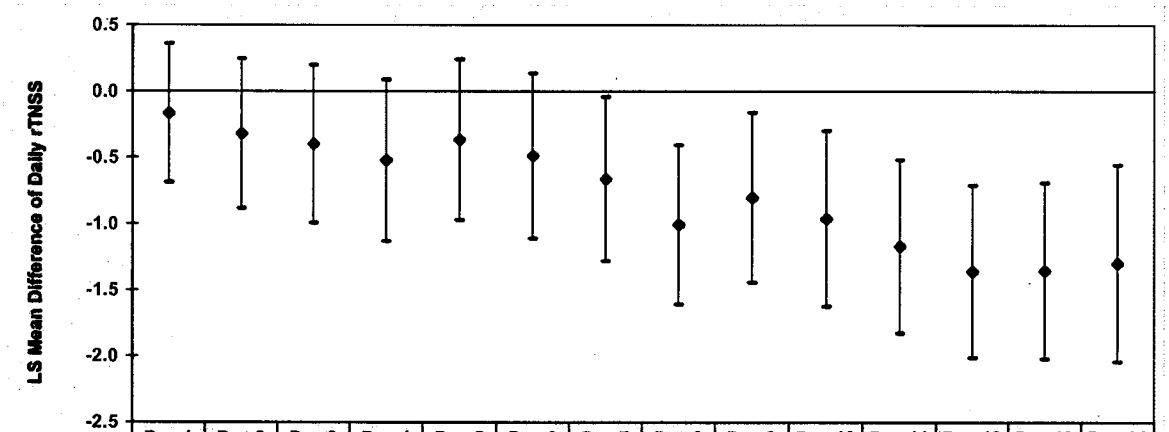



***Assessment of Treatment Effect over Time –***

Figure 7, Figure 8, and Figure 9 show the treatment effect of FF100mcg compared to placebo over 2 weeks for SAR studies. For two out of three studies, the treatment effect started at Day 1 and maintained the magnitude of effect size. For study SAR02, the treatment effect started at Day 7.

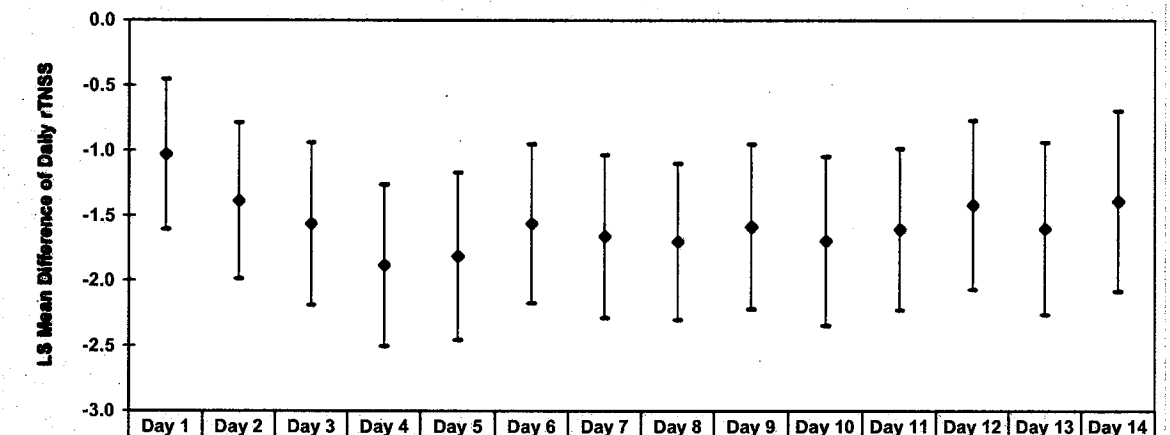
Figure 10 shows the treatment effect of FF100mcg compared to placebo over 4 weeks for PAR study. The treatment effect started at Day 4 and continued to increase until about Day 11.

Figure 7. Treatment Comparison of Change from Baseline of Daily rTNSS by Day, SAR02



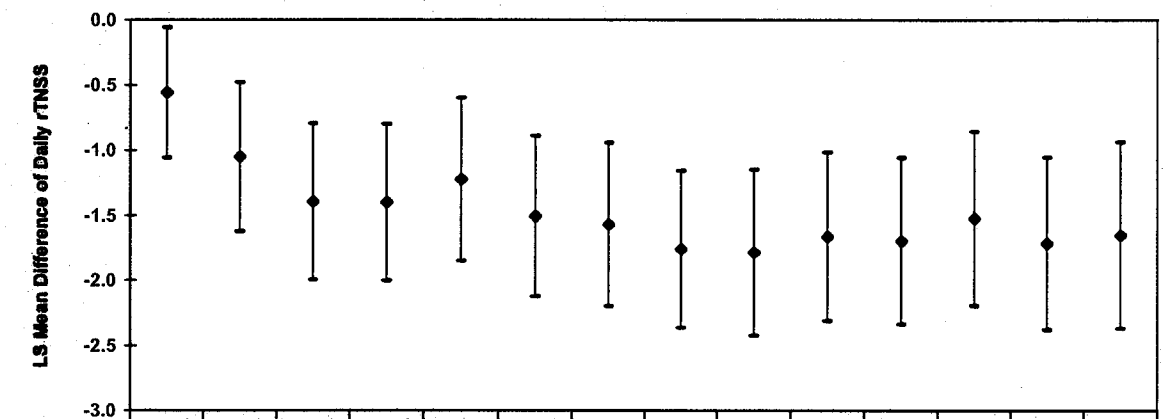

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95%CI - LL | -0.69 | -0.88 | -0.99 | -1.13 | -0.97 | -1.11 | -1.28 | -1.61 | -1.44 | -1.62 | -1.83 | -2.01 | -2.02 | -2.04 |
| - 95%CI - UL | 0.36 | 0.24 | 0.20 | 0.08 | 0.24 | 0.13 | -0.04 | -0.41 | -0.16 | -0.30 | -0.52 | -0.71 | -0.69 | -0.56 |
| ◆FF100 - PL | -0.17 | -0.32 | -0.40 | -0.52 | -0.37 | -0.49 | -0.66 | -1.01 | -0.80 | -0.96 | -1.17 | -1.36 | -1.35 | -1.30 |

Figure 8. Treatment Comparison of Change from Baseline of Daily rTNSS by Day, SAR03



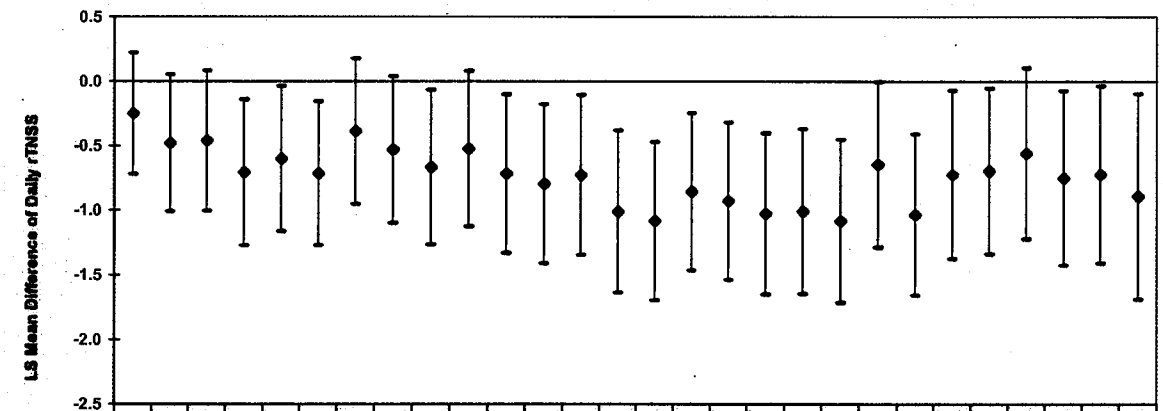

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95%CI - LL | -1.61 | -1.99 | -2.19 | -2.50 | -2.46 | -2.17 | -2.29 | -2.30 | -2.22 | -2.34 | -2.23 | -2.07 | -2.26 | -2.08 |
| - 95%CI - UL | -0.45 | -0.79 | -0.94 | -1.26 | -1.17 | -0.95 | -1.04 | -1.10 | -0.95 | -1.05 | -0.99 | -0.77 | -0.94 | -0.70 |
| ◆FF100 - PL | -1.03 | -1.39 | -1.56 | -1.88 | -1.81 | -1.56 | -1.66 | -1.70 | -1.59 | -1.70 | -1.61 | -1.42 | -1.60 | -1.39 |

Figure 9. Treatment Comparison of Change from Baseline of Daily rTNSS by Day, SAR04




| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95%CI - LL | -1.06 | -1.62 | -1.99 | -2.00 | -1.85 | -2.12 | -2.20 | -2.36 | -2.42 | -2.31 | -2.34 | -2.19 | -2.38 | -2.37 |
| - 95%CI - UL | -0.06 | -0.48 | -0.80 | -0.80 | -0.60 | -0.89 | -0.94 | -1.16 | -1.15 | -1.01 | -1.06 | -0.86 | -1.05 | -0.94 |
| ◆ FF100 - PL | -0.56 | -1.05 | -1.39 | -1.40 | -1.22 | -1.51 | -1.57 | -1.76 | -1.79 | -1.66 | -1.70 | -1.52 | -1.72 | -1.65 |

Figure 10. Treatment Comparison of Change from Baseline of Daily rTNSS by Day, PAR01

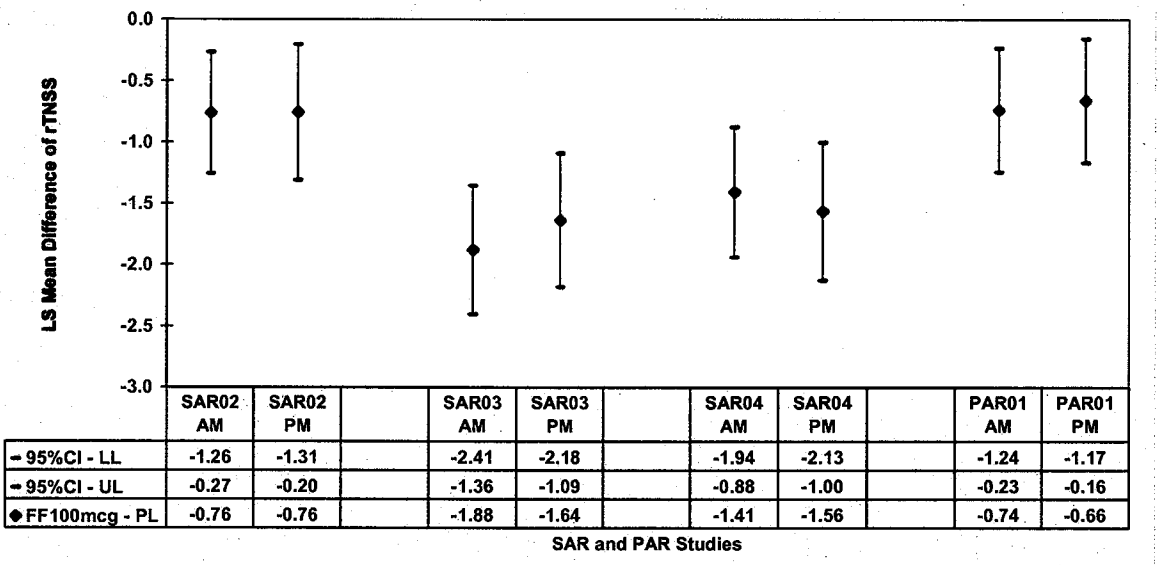



| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Day 20 | Day 21 | Day 22 | Day 23 | Day 24 | Day 25 | Day 26 | Day 27 | Day 28 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95%CI - LL | -0.7 | -1.0 | -1.0 | -1.2 | -1.1 | -1.2 | -0.9 | -1.1 | -1.2 | -1.1 | -1.3 | -1.4 | -1.3 | -1.6 | -1.7 | -1.4 | -1.5 | -1.6 | -1.6 | -1.7 | -1.2 | -1.6 | -1.3 | -1.3 | -1.2 | -1.4 | -1.4 | -1.6 |
| - 95%CI - UL | 0.22 | 0.05 | 0.08 | -0.1 | -0.0 | -0.1 | 0.18 | 0.04 | -0.0 | 0.08 | -0.1 | -0.1 | -0.1 | -0.3 | -0.4 | -0.2 | -0.3 | -0.4 | -0.3 | -0.4 | 0.00 | -0.4 | -0.0 | -0.0 | 0.10 | -0.0 | -0.0 | -0.1 |
| ◆ FF100 - PL | -0.2 | -0.4 | -0.4 | -0.7 | -0.6 | -0.7 | -0.3 | -0.5 | -0.6 | -0.5 | -0.7 | -0.7 | -0.7 | -1.0 | -1.0 | -0.8 | -0.9 | -1.0 | -1.0 | -1.0 | -0.6 | -1.0 | -0.7 | -0.7 | -0.5 | -0.7 | -0.7 | -0.8 |

***Assessment of Treatment Effect over the Full 24-hours –***

Figure 11 displays the treatment comparison of FF100mcg and placebo (given once daily in the morning) in terms of the LS mean change from baseline in AM or PM rTNSS over 2 weeks (SAR) or 4 weeks (PAR). The results show that the magnitude of the treatment difference was similar at both the morning (24-hours post-dose) and the evening (12-hours post-dose) time points.

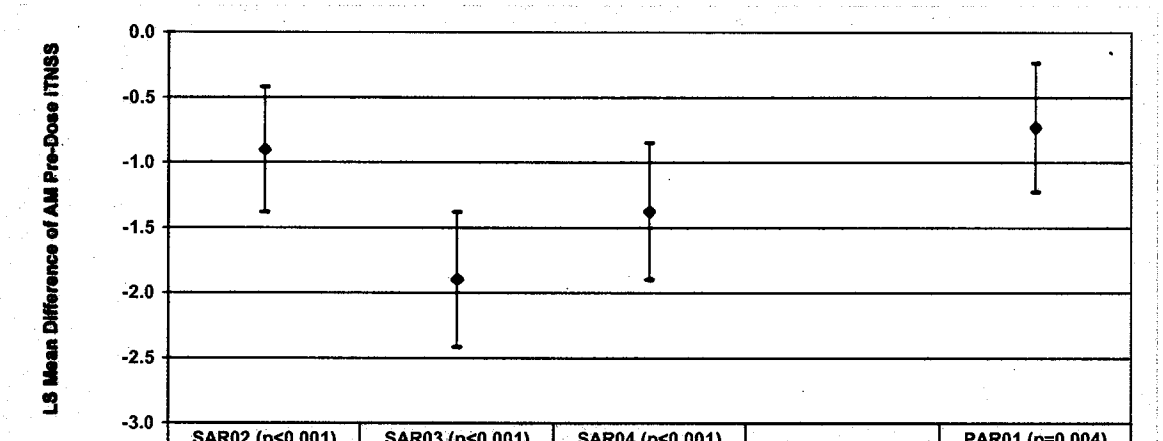
Figure 11. LS Mean Change from Baseline of AM or PM rTNSS




| | SAR02 AM | SAR02 PM | | SAR03 AM | SAR03 PM | | SAR04 AM | SAR04 PM | | PAR01 AM | PAR01 PM |
|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95%CI - LL | -1.26 | -1.31 | | -2.41 | -2.18 | | -1.94 | -2.13 | | -1.24 | -1.17 |
| - 95%CI - UL | -0.27 | -0.20 | | -1.36 | -1.09 | | -0.88 | -1.00 | | -0.23 | -0.16 |
| ◆ FF100mcg - PL | -0.76 | -0.76 | | -1.88 | -1.64 | | -1.41 | -1.56 | | -0.74 | -0.66 |

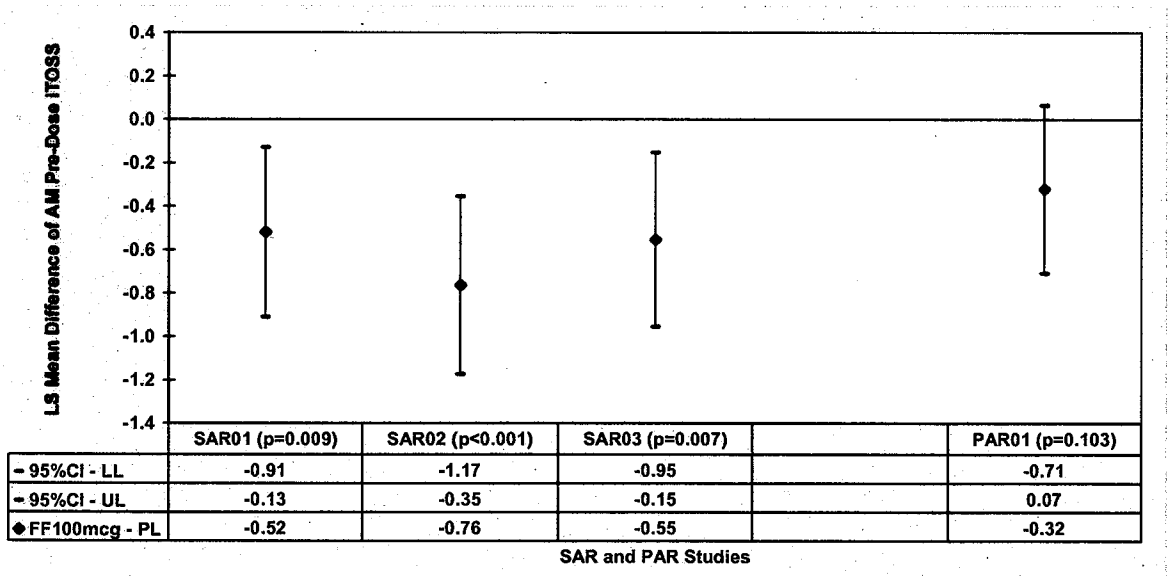
Figure 12 displays the treatment comparison of FF100mcg and placebo in terms of the LS mean change from baseline in AM pre-dose iTNSS and Figure 13 displays the treatment comparison of FF100mcg and placebo in terms of the LS mean change from baseline in AM pre-dose iTOSS. Both results show that the improvement in TNSS was maintained over the full 24-hour dosing interval.

Figure 12. LS Mean Change from Baseline of AM Pre-dose iTNSS




| | SAR02 (p<0.001) | SAR03 (p<0.001) | SAR04 (p<0.001) | | PAR01 (p=0.004) |
|---|---|---|---|---|---|
| - 95%CI - LL | -1.38 | -2.42 | -1.90 | | -1.23 |
| - 95%CI - UL | -0.42 | -1.38 | -0.85 | | -0.24 |
| ◆ FF100mcg - PL | -0.90 | -1.90 | -1.37 | | -0.73 |

Figure 13. LS Mean Change from Baseline of AM Pre-dose iTOSS




*Secondary Efficacy for SAR and PAR –*

**The first key-secondary efficacy endpoint** for SAR and PAR studies was the mean change from baseline over the entire treatment period (2 weeks for SAR studies and 4 weeks for PAR study) in AM pre-dose iTNSS. This reviewer co**nfirmed the sponsor's primary analysis results.** Table 11 displays the analysis results of AM pre-dose iTNSS in the ITT population with randomized treatment which shows that subjects treated with FF100mcg once daily exhibited statistically significant greater decreases in AM pre-dose iTNSS.

Table 11. Change from Baseline in Primary Efficacy Variables: AM Pre-dose iTNSS

| *Treatment* | *Baseline Mean (SD)* | *Change from Baseline* | | *Treatment Comparison FF vs. Placebo* | | |
|---|---|---|---|---|---|---|
| | | N | LS Mean (SE) | LS Mean Difference (SE) | 95% CI | p-value [a] |
| ***AM Pre-dose iTNSS (Day 1-14) SAR02 (scale 0 - 12) – ITT*** | | | | | | |
| FF100mcg | 9.40 (1.60) | 150 | -2.38 (0.20) | -0.90 (0.24) | (-1.38, -0.42) | < 0.001 |
| Placebo | 9.48 (1.51) | 149 | -1.47 (0.20) | - | - | - |
| ***AM Pre-dose iTNSS (Day 1-14) SAR03 (scale 0 - 12) – ITT*** | | | | | | |
| FF100mcg | 8.14 (1.70) | 140 | -4.50 (0.20) | -1.90 (0.26) | (-2.42, -1.38) | <0.001 |
| Placebo | 8.26 (1.70) | 143 | -2.60 (0.19) | - | - | - |
| ***AM Pre-dose iTNSS (Day 1-14) SAR04 (scale 0 - 12) – ITT*** | | | | | | |
| FF100mcg | 9.38 (1.64) | 151 | -2.90 (0.21) | -1.38 (0.27) | (-1.90, -0.85) | <0.001 |
| Placebo | 9.37 (1.60) | 147 | -1.53 (0.21) | - | - | - |
| ***AM Pre-dose iTNSS (Day 1-28) PAR01 (scale 0 - 12) - ITT*** | | | | | | |
| FF100mcg | 8.26 (2.22) | 150 | -2.46 (0.22) | -0.73 (0.25) | (-1.23, -0.24) | 0.004 |
| Placebo | 8.25 (2.08) | 152 | -1.73 (0.21) | - | - | - |

a: p-value is from a repeated measures ANCOVA with treatment, baseline, gender, age, and center.

**The second key-secondary efficacy endpoint** for SAR studies was the mean change from baseline over the entire treatment period (2 weeks) in daily rTOSS. This reviewer confirmed the **sponsor's primary analysis results. Table 12 displa**ys the analysis results of daily rTOSS in ITT population using randomized treatment for SAR studies and PAR study. The results from the SAR studies show that subjects treated with FF100mcg once daily exhibited statistically significant greater decreases in mean daily rTOSS than placebo-treated subjects. The daily rTOSS was not the key secondary efficacy endpoint for PAR study. In an exploratory analysis, the results shows that subjects treated with FF100mcg once daily only a numerically greater decrease in mean daily rTOSS than placebo-treated subjects which did not reach statistical significance.

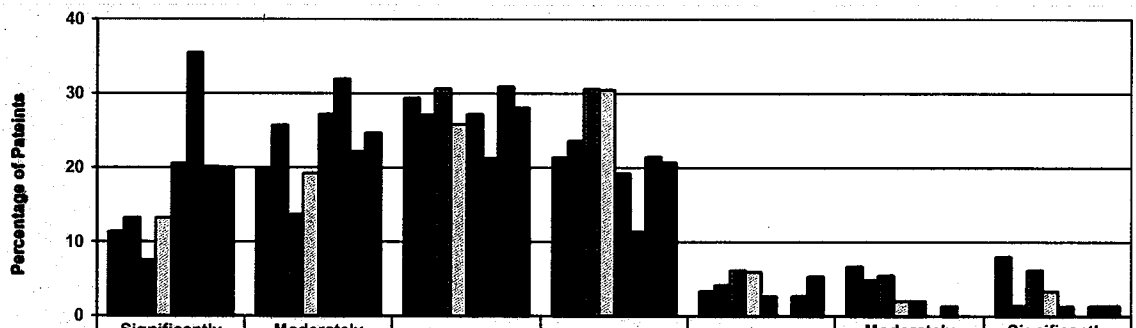
Table 12. Change from Baseline in Primary Efficacy Variables: Daily rTOSS

| ***Treatment*** | ***Baseline Mean (SD)*** | ***Change from Baseline*** | | ***Treatment Comparison FF vs. Placebo*** | | |
|---|---|---|---|---|---|---|
| | | **N** | **LS Mean (SE)** | **LS Mean Difference (SE)** | **95% CI** | **p-value [a]** |
| ***Daily rTOSS (Day 1-14) SAR02 (scale 0 - 9) – ITT*** | | | | | | |
| FF 100mcg | 6.64 (1.34) | 152 | -2.15 (0.16) | -0.55 (0.20) | (-0.95, -0.14) | 0.008 |
| Placebo | 6.52 (1.33) | 150 | -1.60 (0.17) | - | - | - |
| ***Daily rTOSS (Day 1-14) SAR03 (scale 0 - 9) – ITT*** | | | | | | |
| FF 100mcg | 5.37 (1.23) | 140 | -3.00 (0.15) | -0.74 (0.20) | (-1.14, -0.34) | <0.001 |
| Placebo | 5.35 (1.20) | 143 | -2.26 (0.15) | - | - | - |
| ***Daily rTOSS (Day 1-14) SAR04 (scale 0 - 9) – ITT*** | | | | | | |
| FF 100mcg | 6.60 (1.44) | 151 | -2.23 (0.16) | -0.60 (0.21) | (-1.01, -0.19) | 0.004 |
| Placebo | 6.49 (1.47) | 147 | -1.63 (0.16) | - | - | - |
| ***Daily rTOSS (Day 1-28) PAR01 (scale 0 - 9) – ITT[b]*** | | | | | | |
| FF 100mcg | 4.82 (2.29) | 150 | -1.41 (0.16) | -0.19 (0.19) | (-0.56, 0.17) | 0.300 |
| Placebo | 4.96 (2.29) | 152 | -1.22 (0.15) | - | - | - |

a: p-value is from a repeated measures ANCOVA with treatment, baseline, gender, age, and center.
b: The rTOSS test only for exploratory purpose in PAR study.

**The third key-secondary efficacy endpoint** for the SAR and PAR studies was the overall evaluation of response to therapy. At the final study visit, subjects were asked to evaluate their overall response to therapy over the entire treatment period using a 7-point categorical scale. Figure 14 displays the percentage of patients in each category by treatment groups for SAR and PAR studies, in which the blue bars indicate the FF100mcg treatment group and orange bars indicate the placebo treatment group. More patients who received FF100mcg reported being moderately to significantly improved compared with those who received placebo (52% and 30%, respectively, in patients with seasonal allergic rhinitis, and 44% and 33%, respectively, in patients with perennial allergic rhinitis

Figure 14. Percentage of Patients of Overall Evaluation of Response to Therapy




| | Significantly Improved | Moderately Improved | Mildly Improved | No Change | Mildly Worse | Moderately Worse | Significantly Worse |
|---|---|---|---|---|---|---|---|
| SAR02 - PL | 11.3 | 20.0 | 29.3 | 21.3 | 3.3 | 6.7 | 8.0 |
| SAR03 - PL | 13.2 | 25.7 | 27.1 | 23.6 | 4.2 | 4.9 | 1.4 |
| SAR04 - PL | 7.5 | 13.6 | 30.6 | 30.6 | 6.1 | 5.4 | 6.1 |
| PAR01 - PL | 13.2 | 19.2 | 25.8 | 30.5 | 6.0 | 2.0 | 3.3 |
| SAR02 - FF | 20.5 | 27.2 | 27.2 | 19.2 | 2.6 | 2.0 | 1.3 |
| SAR03 - FF | 35.5 | 31.9 | 21.3 | 11.3 | 0.0 | 0.0 | 0.0 |
| SAR04 - FF | 20.1 | 22.1 | 30.9 | 21.5 | 2.7 | 1.3 | 1.3 |
| PAR01 - FF | 20.0 | 24.7 | 28.0 | 20.7 | 5.3 | 0.0 | 1.3 |

**The fourth key-secondary efficacy endpoint** for SAR and PAR studies was RQLQ. Original RQLQ data was submitted with NDA submission on 28 June, 2006. On September 13, 2006, the sponsor submitted corrected RQLQ data for three SAR studies and PAR study (See attachment 6.1 for details). The sponsor had taken the approach regarding RQLQ analysis in which the activity domain scores at endpoint were set as missing if text entries did not match 100% at baseline and final visit, resulting in a high percentage of missing values (26% - 52%) for the activity domain scores in the SAR and PAR studies. This reviewer found the problem and had a meeting with the sponsor in November, 2006. In light of this high proportion of missing data, this reviewer recommended to re-analyze the RQLQ data utilizing also the activity domain score where the text entries have the same meaning at baseline and endpoint even if they do not match 100% (e.g. walk, walking, gone walking, and taking a walk have different test string but have the same meaning) and asked the sponsor that if upon re-analysis the missing rate for a given study was still > 25%, a sensitivity analysis should be performed where imputation should be employed for the missing activity scores at endpoint. The sponsor submitted the re-analysis of RQLQ and the revised data on December 13, 2006. (See attachment 6.2 for details)

The sponsor did not pre-specify the missing data handling for RQLQ individual domain questionnaire in study protocol and SAP. In the submission on December 13, 2006, sponsor did the Analysis of Mean Change from Baseline to Endpoint in RQLQ Scores based on three datasets: 1. the Modified RQLQ dataset without imputation on missing activity scores; 2. the modified RQLQ dataset with imputing missing scores if there were at lease two non-missing activity scores; 3. the modified RQLQ dataset with imputing missing scores if there was at least one non-missing activity score ( see corresponding results in Table 13 columns 1, 2, and 3)

This review confirmed the sponsor's re-analysis results. The estimated treatment effect from re-analysis and sensitivity analyses was compared to the results provided in NDA22-051 amendment dated September 13, 2006, and summarized in Table 13. For the overall RQLQ score, missing data on the activity domain did not have any material impact on the analysis results, regardless of the imputation methods.

Table 13. Summary of Analysis Results for the Overall Score and the Activity Domain of RQLQ

| | | ***Analysis in NDA Amendment*** | ***Re-Analysis (1)*** | ***Sensitivity Analysis #1 (2)*** | ***Sensitivity Analysis #2 (3)*** |
|---|---|---|---|---|---|
| | | LSM.Diff (p-value) | LSM.Diff (p-value) | LSM.Diff (p-value) | LSM.Diff (p-value) |
| **SAR02** | | | | | |
| | **Overall** | -0.69 (<0.001) | -0.69 (<0.001) | -0.69 (<0.001) | -0.69 (<0.001) |
| | **Activities** | -0.64 (0.034) | -0.72 (0.003) | -0.65 (0.006) | -0.67 (0.005) |
| **SAR03** | | | | | |
| | **Overall** | -0.70 (<0.001) | -0.70 (<0.001) | -0.70 (<0.001) | -0.70 (<0.001) |
| | **Activities** | -0.90 (<0.001) | -0.89 )<0.001_ | -0.90 (<0.001) | -0.85 (<0.001) |
| **SAR04** | | | | | |
| | **Overall** | -0.60 (<0.001) | -0.60 (<0.001) | -0.60 (<0.001) | -0.61 (<0.001) |
| | **Activities** | -0.59 (0.027) | -0.72 (<0.001) | -0.77 (<0.001) | -0.80 (<0.001) |
| **PAR01** | | | | | |
| | **Overall** | -0.25 (0.215) | -0.23 (0.214) | -0.23 (0.214) | -0.23 (0.200) |
| | **Activities** | 0.02 (0.953) | -0.01 (0.960) | -0.03 (0.917) | -0.16 (0.517) |

LSM.Diff = LS Mean Difference

Table 14 displays the ratio of number of subjects with missing scores over the number of subjects with non-missing scores in each domain for four studies. Study SAR03 still has more than 25% missing records in the activity domain.

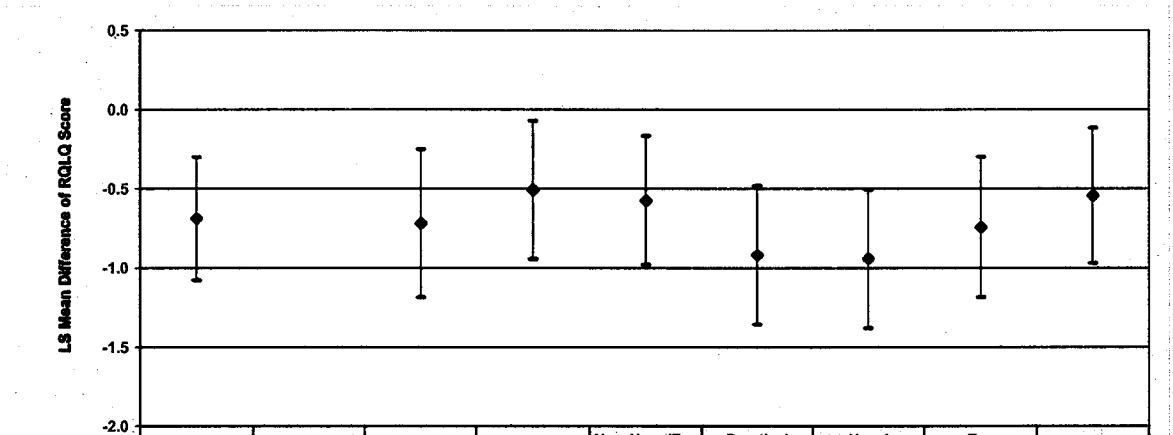
Table 14. Ratio of Subjects with Missing to Non-missing Change from Baseline RQLQ Scores

| ***Study*** | ***TRT*** | ***Overall*** | ***Activities*** | ***Sleep*** | ***Non Nose/Eye Symptoms*** | ***Practical Problems*** | ***Nasal Symptoms*** | ***Eye Symptoms*** | ***Emotional*** |
|---|---|---|---|---|---|---|---|---|---|
| **SAR02** | FF | 2/149 | 16/135 | 0/151 | 0/151 | 1/150 | 1/150 | 3/148 | 2/149 |
| | PL | 1/149 | 17/133 | 2/148 | 1/149 | 1/149 | 1/149 | 1/149 | 1/149 |
| **SAR03** | FF | 3/137 | 49/91 | 2/138 | 2/138 | 4/136 | 2/138 | 3/137 | 3/137 |
| | PL | 4/140 | 48/96 | 5/139 | 4/140 | 4/140 | 6/138 | 4/140 | 4/140 |
| **SAR04** | FF | 5/144 | 37/112 | 2/147 | 3/146 | 3/146 | 5/144 | 5/144 | 5/144 |
| | PL | 4/144 | 31/117 | 3/145 | 3/145 | 4/144 | 4/144 | 4/144 | 5/143 |
| **PAR01** | FF | 2/144 | 26/120 | 2/144 | 5/141 | 5/141 | 4/142 | 2/144 | 2/144 |
| | PL | 0/150 | 24/126 | 1/149 | 0/150 | 0/150 | 1/149 | 1/149 | 0/150 |

Figure 15, Figure 16, Figure 17, and Figure 18 display the comparison of mean changed from baseline of individual seven domains score and overall score based on the dataset submitted on NDA22-051 amendment dated September 13, 2006. No difference was observed at baseline between subjects assigned FF100mcg or placebo for any of the domain scores or the overall scores of the RQLQ. Comparing the difference of the LS mean change from baseline to endpoint between the two groups, subjects assigned to FF100mcg QD experienced statistically significant and a minimally important difference (greater improvement of at least -0.5 over

placebo) in overall RQLQ scores, and in each of the seven individual domains (except Non-Nose/Eye Symptoms in SAR03 and Eye Symptoms in SAR04) compared to placebo for SAR studies. For PAR study FF100mcg QD did not reach statistical significance and did not meet the minimally important difference.

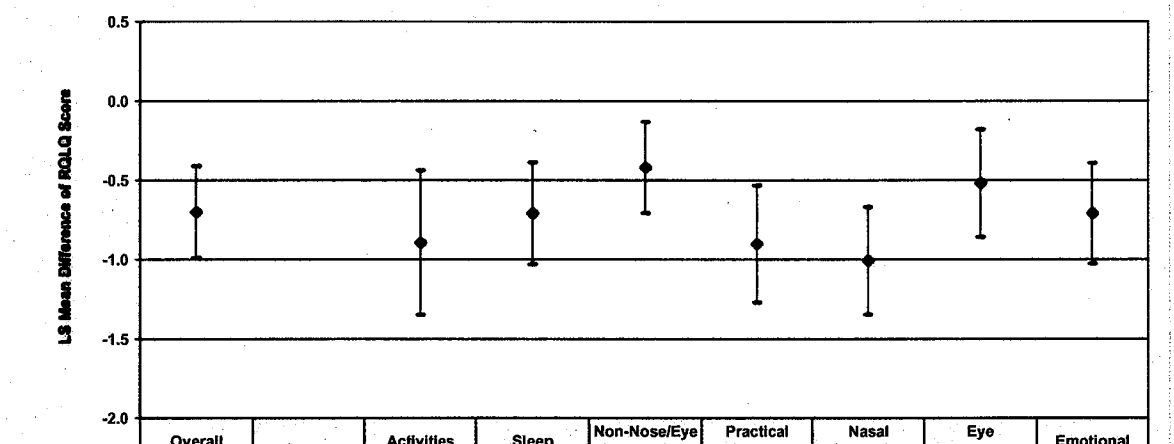
Figure 15. LS Mean and 95% CI of Response of RQLQ Individual Domain and Overall, SAR02




| | Overall | | Activities | Sleep | Non-Nose/Eye Symptoms | Practical Problems | Nasal Symptoms | Eye Symptoms | Emotional |
|---|---|---|---|---|---|---|---|---|---|
| 95% CI - LL | -1.08 | | -1.19 | -0.95 | -0.98 | -1.36 | -1.38 | -1.19 | -0.97 |
| 95% CI - UL | -0.30 | | -0.25 | -0.07 | -0.17 | -0.48 | -0.51 | -0.30 | -0.12 |
| FF100mcg - PL | -0.69 | | -0.72 | -0.51 | -0.57 | -0.92 | -0.94 | -0.74 | -0.54 |

RQLQ 7 Domains and Overall Score

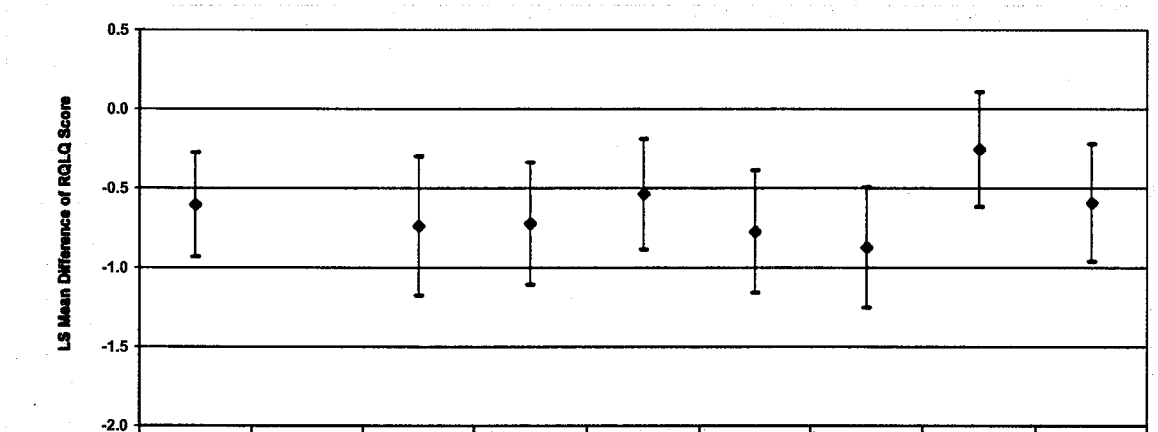
Figure 16. LS Mean and 95% CI of Response of RQLQ Individual Domain and Overall, SAR03




| | Overall | | Activities | Sleep | Non-Nose/Eye Symptoms | Practical Problems | Nasal Symptoms | Eye Symptoms | Emotional |
|---|---|---|---|---|---|---|---|---|---|
| 95% CI - LL | -0.99 | | -1.35 | -1.03 | -0.71 | -1.27 | -1.35 | -0.86 | -1.03 |
| 95% CI - UL | -0.41 | | -0.44 | -0.39 | -0.13 | -0.53 | -0.67 | -0.18 | -0.39 |
| FF100mcg - PL | -0.70 | | -0.89 | -0.71 | -0.42 | -0.90 | -1.01 | -0.52 | -0.71 |

RQLQ 7 Domains and Overall Score

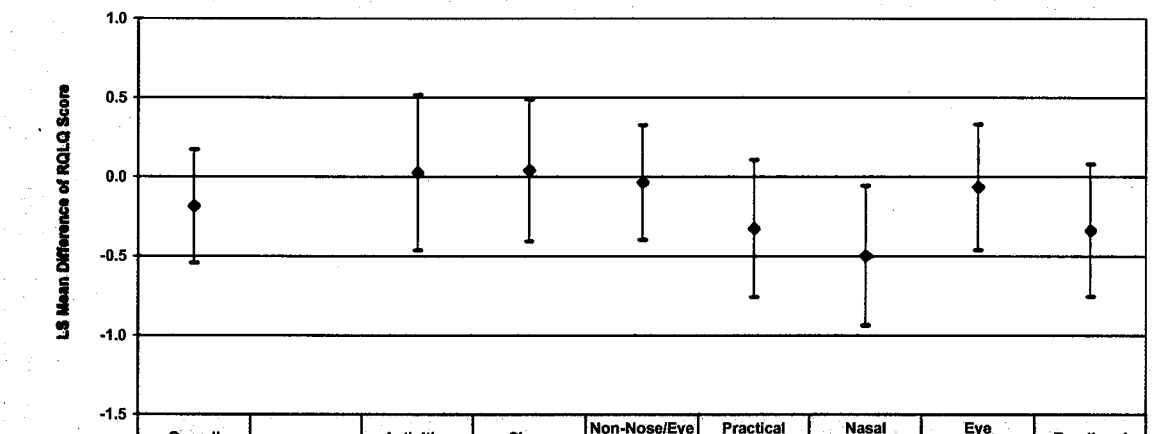
Figure 17. LS Mean and 95% CI of Response of RQLQ Individual Domain and Overall, SAR04




| | Overall | | Activities | Sleep | Non-Nose/Eye Symptoms | Practical Problems | Nasal Symptoms | Eye Symptoms | Emotional |
|---|---|---|---|---|---|---|---|---|---|
| 95% CI - LL | -0.93 | | -1.18 | -1.11 | -0.89 | -1.16 | -1.25 | -0.62 | -0.96 |
| 95% CI - UL | -0.28 | | -0.30 | -0.34 | -0.19 | -0.39 | -0.49 | 0.11 | -0.22 |
| FF100mcg - PL | -0.60 | | -0.74 | -0.72 | -0.54 | -0.77 | -0.87 | -0.25 | -0.59 |

RQLQ 7 Domains and Overall Score

Figure 18. LS Mean and 95% CI of Response of RQLQ Individual Domain and Overall, PAR01




| | Overall | | Activities | Sleep | Non-Nose/Eye Symptoms | Practical Problems | Nasal Symptoms | Eye Symptoms | Emotional |
|---|---|---|---|---|---|---|---|---|---|
| 95% CI - LL | -0.54 | | -0.46 | -0.41 | -0.40 | -0.76 | -0.94 | -0.46 | -0.76 |
| 95% CI - UL | 0.17 | | 0.52 | 0.49 | 0.32 | 0.11 | -0.06 | 0.33 | 0.08 |
| FF100mcg - PL | -0.19 | | 0.03 | 0.04 | -0.04 | -0.33 | -0.50 | -0.06 | -0.34 |

RQLQ 7 Domains and Overall Score

***Individual Symptoms Scores of TNSS –***

The changes from baseline of daily reflective symptom scores for individual symptoms of the TNSS over 14-days (SAR studies) or 28-days (PAR study) are summarized in Table 15, which shows the patients treated with FF100mcg had improvements versus placebo in all four nasal symptoms except nasal congestion and itchy nose which did not reach statistical significance in

study PAR01 and itchy nose which did not reach statistical significance in study SAR02.

Table 15. Change from Baseline in Average AM and PM Reflective Individual Symptoms Score

| Study | N | | Baseline (Mean ± SD) | | Change from Baseline (LS Mean ± SE) | | LS Mean Difference, P-value, 95%CI |
|---|---|---|---|---|---|---|---|
| | FF | PL | FF | PL | FF | PL | FF - PL |
| **Daily Individual rTNSS – Itchy Nose (Scale 0 to 3)** | | | | | | | |
| SAR02[1] | 152 | 150 | 2.51 (0.41) | 2.47 (0.41) | -0.75 (0.06) | -0.61 (0.06) | -0.14, p=0.063, (-0.28, 0.01) |
| SAR03[1] | 140 | 143 | 2.00 (0.50) | 2.00 (0.48) | -1.19 (0.06) | -0.82 (0.05) | -0.37, p<.001 (-0.52, -0.23) |
| SAR04[1] | 151 | 147 | 2.45 (0.48) | 2.47 (0.52) | -0.86 (0.06) | -0.52 (0.06) | -0.34, p<.001 (-0.45, -0.20) |
| PAR01[2] | 149 | 153 | 2.09 (0.71) | 2.09 (0.65) | -0.69 (0.06) | -0.53 (0.06) | -0.16, p=0.024 (-0.30, -0.02) |
| **Daily Individual rTNSS – Nasal Congestion (Scale 0 to 3)** | | | | | | | |
| SAR02[1] | 152 | 150 | 2.62 (0.36) | 2.63 (0.35) | -0.75 (0.05) | -0.58 (0.05) | -0.17, p=0.012 (-0.30, -0.04) |
| SAR03[1] | 140 | 143 | 2.36 (0.35) | 2.37 (0.34) | -1.30 (0.05) | -0.82 (0.05) | 09,49, p<0.0001 (-0.63, -0.34) |
| SAR04[1] | 151 | 147 | 2.63 (0.37) | 2.64 (0.36) | -0.84 (0.06) | -0.48 (0.06) | -0.36, p<0.001 (-0.50, -0.22) |
| PAR01[2] | 149 | 153 | 2.54 (0.37) | 2.75 (0.59) | -0.70 (0.06) | -0.58 (0.06) | -0.12, p=0.092 (-0.27, 0.02) |
| **Daily Individual rTNSS – Runny Nose (Scale 0 to 3)** | | | | | | | |
| SAR02[1] | 152 | 150 | 2.50 (0.44) | 2.47 (0.43) | -0.77 (0.06) | -0.56 (0.06) | -0.21, p=0.004 (-0.35, -0.07) |
| SAR03[1] | 140 | 143 | 2.07 (0.54) | 2.12 (0.51) | -1.26 (0.05) | -0.78 (0.05) | -0.48, p<.0001 (-0.62, -0.34) |
| SAR04[1] | 151 | 147 | 2.41 (0.52) | 2.50 (0.45) | -0.87 (0.06) | -0.54 (0.06) | -0.33, p<.001 (-0.48, -0.18) |
| PAR01[2] | 149 | 153 | 2.26 (0.54) | 2.16 (0.63) | -0.72 (0.06) | -0.52 (0.06) | -0.20. p <0.001 (-0.34, -0.06) |
| **Daily Individual rTNSS – Sneezing (Scale 0 to 3)** | | | | | | | |
| SAR02[1] | 152 | 150 | 2.22 (0.56) | 2.17 (0.58) | -0.77 (0.06) | -0.51 (0.06) | -0.26 p<0.001 (-0.41, -0.12) |
| SAR03[1] | 140 | 143 | 1.94 (0.57) | 1.89 (0.51) | -1.20 (0.05) | -0.76 (0.05) | -0.44, p<.001 (-0.58, -0.30) |
| SAR04[1] | 151 | 147 | 2.15 (0.67) | 2.38 (0.59) | -0.99 (0.06) | -0.52 (0.06) | -0.48, p<.001 (-0.63, -0.32) |
| PAR01[2] | 149 | 153 | 1.75 (0.76) | 1.83 (0.76) | -0.68 (0.06) | -0.45 (0.05) | -0.23, p= 0.001 (-0.37, -0.09) |

1: Average of 14-days; 2: Average of 28-days.

***Conclusion –***

The efficacy evaluation of four phase-III, randomized, multi-center, double-blind, parallel-group, and placebo-control studies (SAR02, SAR03, SAR04 and PAR01), demonstrated that Fluticasone Furoate Nasal Spray 27.5mcg is statistically significantly superior to placebo in improving the reflective Total Nasal Symptoms Score (rTNSS) after a dosage regimen of two sprays per nostril once daily (100mcg per day, hereafter referred to FF100mcg) in adult and adolescent patients 12 years and older with SAR or PAR. The efficacy evaluation of study SAR01, the phase-II, randomized, multi-center, double-blind, parallel-group, and placebo-control, and dose-finding study, demonstrated that FF four dose regimens (50, 100, 200, and 400mcg) were all statistically significantly superior to placebo in improving the Total Nasal

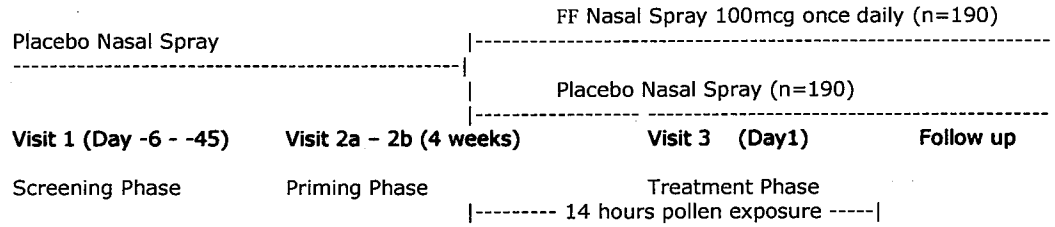
Symptoms Score.
The efficacy of FF100mcg in the treatment of SAR subjects was supported by the key secondary endpoints of AM pre-dose instantaneous Total Nasal Symptoms Score (iTNSS), daily reflective Total Ocular Symptoms (rTOSS), the overall evaluation of response to therapy, and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). For PAR subjects, the treatment difference between FF100mcg and placebo did not reach statistical significance for both rTOSS and RQLQ.

### *3.1.2 Allergen Challenge Chamber Study (SAR05)*

#### 3.1.2.1 Design

Study SAR05 was a randomized, double-blind, placebo-controlled, parallel-group, single-dose study, conducted in Marietta, Georgia, to evaluate the onset of action of a single dose of FF100mcg in adolescent and adult subjects (≥ 12 years of age) with SAR exposed to ragweed pollen in an allergen challenge chamber. (See the study flow charts below.)

**Study SAR05**




The time to onset of action was defined as the first time after the initiation of the treatment at which a statistically significant greater change in AM pre-dose iTNSS is achieved for FF100 mcg versus placebo and the treatment effect is sustained from this time point onward during the 12-hour post-dose exposure period in allergen chamber exposure.

The primary analysis method was the comparison of treatment groups at each time point (active vs. placebo) using a repeated measures model, adjusting for baseline iTNSS, age, gender, session, treatment, time, and treatment by time interaction. Unstructured correlation structure was selected to account for the repeated measures. Mean change from baseline in iTNSS was illustrated over time (hour 1 through hour 12) by treatment group. The least squares mean changes for each treatment group was summarized and compared. The 95% confidence interval (CI) for the treatment mean difference (active vs. placebo) was also reported, as well as the p-values corresponding to the test of significance for the treatment mean difference.

In Study SAR05, a sample size of 190 patients per treatment group was sufficient to provide 90% power to demonstrate a difference of 0.75 at any time point in iTNSS using a two-sided alpha level of 0.05. In this study the standard deviation for the change from baseline in iTNSS ranged from 2.1 to 2.7. This corresponds to a power to demonstrate a difference of 0.75 at any

time point ranging from 77% to 93%. The observed sample size was 381 total, so the trial was adequately powered.

Onset of action of FF100mcg once daily was also investigated in three phase III SAR studies and one dose-finding SAR study (SAR01, SAR02, SAR03, and SAR04), as well as via the single-dose Environmental Exposure Unit/Chamber Study (SAR05). For this review, the results for time to onset of action for study SAR05 are posted with the results from the four SAR studies.

#### 3.1.2.2 Sponsor's Results and Conclusions

The sponsor concluded that (page 149, ise.pdf)
***"Onset of action was observed at 8 hours after initial administration in two clinical studies in SAR (FFR20001 and FFR104861), as evaluated by mean AM pre-dose iTNSS. In a third SAR study (FFR103814), a significant improvement in nasal symptoms occurred within the first day (12 to 24 hours) following initial administration. In the fourth SAR study (FFR30003), a significant difference in mean AM pre-dose iTNSS compared with placebo was observed at 24 hours, but was not consistently maintained until Day 6."***

#### 3.1.2.3 Reviewer's Efficacy Analysis s

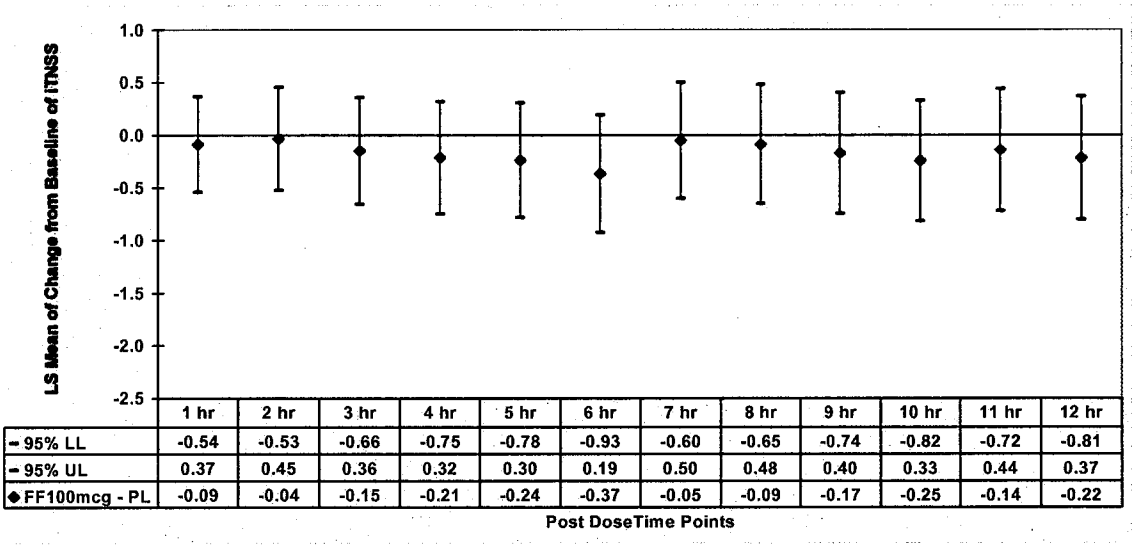
Table 16 summarizes the results of the primary **efficacy analysis – hourly assessment of iTNSS** on Day 1 and daily assessment of iTNSS on Day 2 Day 3, Day 4, and Day 5. Two out of four SAR studies (SAR01 and SAR04) demonstrated onset of action at Hour 8 and two out of four SAR studies (SAR02 and SAR03) demonstrated the onset of action at Hour 24. The ACC study **(SAR05) didn't show the onset of** action at any time point. Figure 19, Figure 20, and Figure 21 display the LS mean of Change from baseline of AM pre-dose iTNSS by hour.

Table 16. Hourly Assessment of iTNSS on Day1- Day 5 (LS Mean of FF100 - Placebo)

| | ***SAR01 (n=255)*** | ***SAR02 (n=303)*** | ***SAR03 (n=285)*** | ***SAR04 (n=299)*** | ***SAR05 (n=381)*** |
|---|---|---|---|---|---|
| ***Hour*** | **LS Mean Diff. p-value[1]** | **LS Mean Diff. p-value** | **LS Mean Diff. p-value** | **LS Mean Diff. p-value** | **LS Mean Diff. p-value** |
| **Hour 1** | - | - | - | - | -0.09, $p$=0.70 |
| **Hour 2** | - | - | - | - | -0.04, $p$=0.89 |
| **Hour 3** | - | - | - | - | -0.15, $p$=0.56 |
| **Hour 4** | -0.59, $p$=0.060 | -0.08, $p$=0.784 | -0.52, $p$=0.077 | -0.06, $p$=0.844 | -0.21, $p$=0.43 |
| **Hour 5** | - | - | - | - | -0.24, $p$=0.39 |
| **Hour 6** | - | -0.16, $p$=0.592 | -0.23, $p$=0.456 | -0.28, $p$=0.355 | -0.37, $p$=0.19 |
| **Hour 7** | - | - | - | - | -0.05, $p$=0.85 |
| **Hour 8** | -0.71, $p$=0.031 | -0.06, $p$=0.855 | -0.51, $p$=0.118 | -0.75, $p$=0.018 | -0.09, $p$=0.76 |
| **Hour 9** | - | - | - | - | -0.17, $p$=0.56 |
| **Hour 10** | - | -0.16, $p$=0.613 | -0.60, $p$=0.078 | -0.83, $p$=0.009 | -0.25, $p$=0.40 |
| **Hour 11** | - | - | - | - | -0.14, $p$=0.63 |
| **Hour 12** | -1.11, $p$=0.002 | -0.41, $p$=0.216 | -0.67, $p$=0.063 | -0.55, $p$=0.099 | -0.22, $p$=0.46 |
| **Hour 24** | -1.27, $p$<0.001 | -0.53, $p$=0.045 | -1.24, $p$<0.001 | -0.75, $p$=0.006 | - |
| **Day 2** | -1.41, $p$<0.001 | -0.70, $p$=0.016 | -1.63, $p$<0.001 | -0.94, $p$=0.002 | - |
| **Day 3** | -1.37, $p$<0.001 | -0.44, $p$=0.162 | -1.82, $p$<0.001 | -1.17, $p$<0.001 | - |
| **Day 4** | -1.69, $p$<0.001 | -0.73, $p$=0.018 | -1.96, $p$<0.001 | -1.35, $p$<0.001 | - |
| **Day 5** | -1.84, $p$<0.001 | -0.56, $p$=0.061 | -1.95, $p$<0.001 | -1.11, $p$<0.001 | - |

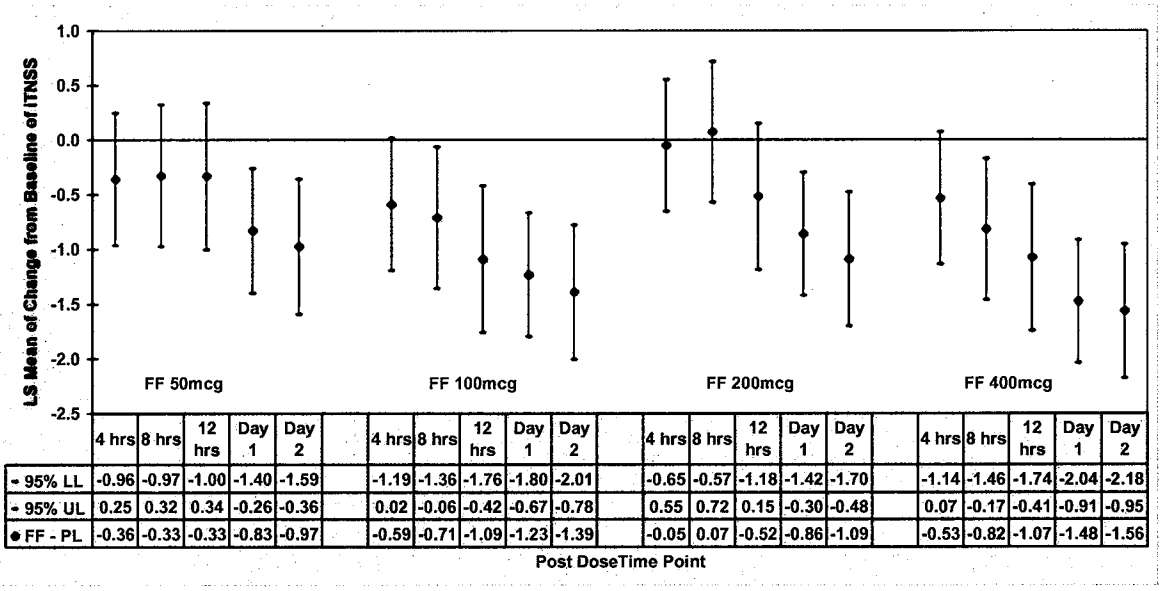
1. p-value is from comparison of treatment groups using ANCOVA at each time point with covariate adjustment for age, gender, center, treatment, and baseline. Baseline is the Hour 0 assessment. 2. The highlight indicated the first significant time-point and confirmed time-point.

Figure 19. Change from Baseline of iTNSS After Dose Study SAR05



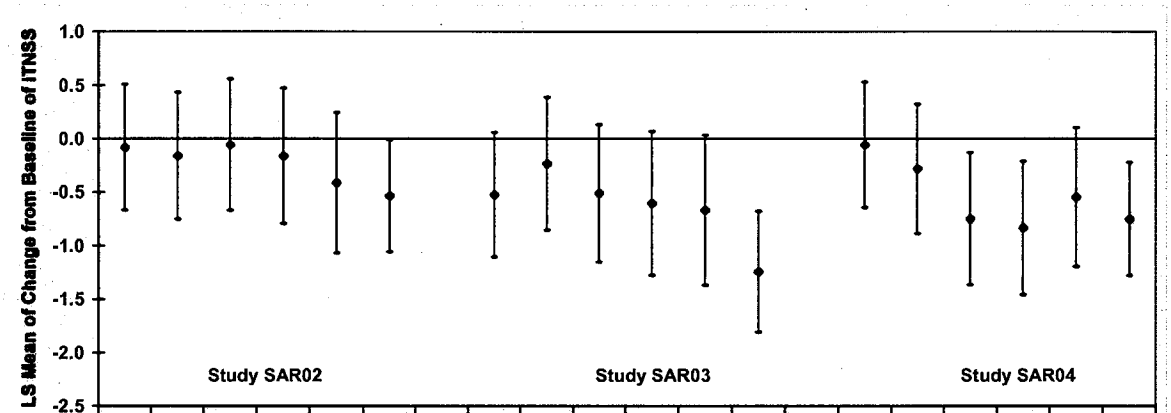

| | 1 hr | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 7 hr | 8 hr | 9 hr | 10 hr | 11 hr | 12 hr |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95% LL | -0.54 | -0.53 | -0.66 | -0.75 | -0.78 | -0.93 | -0.60 | -0.65 | -0.74 | -0.82 | -0.72 | -0.81 |
| - 95% UL | 0.37 | 0.45 | 0.36 | 0.32 | 0.30 | 0.19 | 0.50 | 0.48 | 0.40 | 0.33 | 0.44 | 0.37 |
| ◆ FF100mcg - PL | -0.09 | -0.04 | -0.15 | -0.21 | -0.24 | -0.37 | -0.05 | -0.09 | -0.17 | -0.25 | -0.14 | -0.22 |

Figure 20. Change from Baseline of Post-Dose iTNSS, SAR01




| | 4 hrs | 8 hrs | 12 hrs | Day 1 | Day 2 | | 4 hrs | 8 hrs | 12 hrs | Day 1 | Day 2 | | 4 hrs | 8 hrs | 12 hrs | Day 1 | Day 2 | | 4 hrs | 8 hrs | 12 hrs | Day 1 | Day 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95% LL | -0.96 | -0.97 | -1.00 | -1.40 | -1.59 | | -1.19 | -1.36 | -1.76 | -1.80 | -2.01 | | -0.65 | -0.57 | -1.18 | -1.42 | -1.70 | | -1.14 | -1.46 | -1.74 | -2.04 | -2.18 |
| - 95% UL | 0.25 | 0.32 | 0.34 | -0.26 | -0.36 | | 0.02 | -0.06 | -0.42 | -0.67 | -0.78 | | 0.55 | 0.72 | 0.15 | -0.30 | -0.48 | | 0.07 | -0.17 | -0.41 | -0.91 | -0.95 |
| ◆ FF - PL | -0.36 | -0.33 | -0.33 | -0.83 | -0.97 | | -0.59 | -0.71 | -1.09 | -1.23 | -1.39 | | -0.05 | 0.07 | -0.52 | -0.86 | -1.09 | | -0.53 | -0.82 | -1.07 | -1.48 | -1.56 |

Figure 21. Change from Baseline of Post-Dose iTNSS SAR Studies




| | Study SAR02 | | | | | | Study SAR03 | | | | | | Study SAR04 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 4 hrs | 6 hrs | 8 hrs | 10 hrs | 12 hrs | 24 hrs | 4 hrs | 6 hrs | 8 hrs | 10 hrs | 12 hrs | 24 hrs | 4 hrs | 6 hrs | 8 hrs | 10 hrs | 12 hrs | 24 hrs |
| - 95% LL | -0.67 | -0.75 | -0.67 | -0.80 | -1.07 | -1.06 | -1.11 | -0.85 | -1.15 | -1.28 | -1.37 | -1.81 | -0.64 | -0.89 | -1.37 | -1.46 | -1.20 | -1.28 |
| - 95% UL | 0.51 | 0.43 | 0.56 | 0.47 | 0.24 | -0.01 | 0.06 | 0.38 | 0.13 | 0.07 | 0.04 | -0.68 | 0.53 | 0.32 | -0.13 | -0.21 | 0.10 | -0.22 |
| • FF - PL | -0.08 | -0.16 | -0.06 | -0.16 | -0.41 | -0.53 | -0.52 | -0.23 | -0.51 | -0.60 | -0.67 | -1.24 | -0.06 | -0.28 | -0.75 | -0.83 | -0.55 | -0.75 |

Post Dose Time Point

***Conclusion –***

The efficacy evaluation of study SAR05, the allergen challenge chamber (ACC) study, did not demonstrate any onset of action. The onset of action was only observed at 8 hours after initial administration in two out of four SAR studies. The onset of action was consistently seen after 24 hours in all the Phase 3 studies. The improvement in AM pre-dose iTNSS was maintained over the full 24-hour dosing interval.

### *3.1.3 Pediatric Studies (PED01 and PED02)*

#### 3.1.3.1 Design

The objective of these studies was to evaluate the efficacy and safety of FF at two dose levels (100 or 50mcg, once daily) versus placebo in the treatment of SAR or PAR in pediatric patients (ages 2-11 years old). Studies PED01 and PED02 had the same design, which was a phase III randomized, double-blind, parallel-group, placebo-controlled, multi-national, multi-center, and multi-dose study to evaluate the efficacy and safety of once-daily, intranasal administration of FF 50 and 100mcg administered for 2 weeks (PED01) and 12 weeks (PED02) in pediatric patients 2-11 years of age with SAR (PED01) or PAR (PED02). Patients were randomized to 1 of 3 arms (placebo, FF 50, 100mcg/day) in a ratio of 1:1:1.

#### 3.1.3.2 Patients Disposition

As indicated in Table 17, a total of 554 subjects (ITT population) who satisfied the inclusion and exclusion criteria were randomly assigned to receive FF100mcg, 50mcg once daily, or placebo in

Study PED01. Five hundred and thirty sex subjects (97%) completed this study. The percent of subject who discontinued was similar in all the treatment groups in this study.

Again referring to Table 17, a total of 558 subjects (ITT population) who satisfied the inclusion and exclusion criteria were randomly assigned to receive FF 100mcg, 50mcg once daily and placebo in Study PED02. Four hundred and ninety two subjects (88%) completed their study. The percent of subjects who discontinued was slightly higher in the placebo group (14%) than FF 100mcg groups (9%).

**Table 17. ITT Patients' Accountability** N (%), Studies for PED01, PED02

| | ***PED01 (n=554) 2-weeks*** | | | ***PED02 (n=558) 12-weeks*** | | |
|---|---|---|---|---|---|---|
| | ***Placebo*** | ***FF 50mcg*** | ***FF 100mcg*** | ***Placebo*** | ***FF 50mcg*** | ***FF 100mcg*** |
| Entered | 186 | 186 | 184 | 188 | 185 | 185 |
| Completed | 180 (96.8) | 175 (94.1) | 181 (98.4) | 161 (85.6) | 163 (88.1) | 168 (90.8) |
| Discontinued | 6 (3.2) | 9 (5.9) | 3 (1.6) | 27 (14.4) | 22 (11.9) | 17 (9.2) |
| ***Reason of early discontinuation[1]*** | | | | | | |
| Adverse Event | 4 | 4 | 2 | 8 | 6 | 2 |
| Protocol violation | 1 | 0 | 1 | 4 | 5 | 6 |
| Lack of Efficacy | 0 | 0 | 0 | 0 | 0 | 1 |
| Pt. Withdraw Consent | 1 | 4 | 0 | 6 | 4 | 2 |
| Lost Follow-up | 0 | 0 | 0 | 2 | 2 | 4 |
| Sponsor terminated study | 0 | 0 | 0 | 0 | 1 | 1 |
| Others | 0 | 1 | 0 | 7 | 4 | 1 |
| ***Analysis Population*** | | | | | | |
| ITT | 184 | 183 | 184 | 179 | 183 | 181 |

Some patient discontinued for more than one reasons. Data: Dispos.xpt; Code: Demog.sas.

The demographics and baseline characteristics for all randomized patients (ITT) for Study PED01 and PED02 are summarized in Table 18. The majority of the subjects were Caucasian (80% in Study PED01 and 73% in Study PED02) and 6 to < 12 years old (80% in both studies). The demographic and baseline characteristics were balanced across treatment groups in both studies.

Table **18. ITT Subjects' Demographics** and Baseline Characteristics, Studies for SAR and PAR

| | ***PED01 (n=554) SAR*** | | | ***PED405 (n=558) PAR*** | | |
|---|---|---|---|---|---|---|
| | ***Placebo (n=186)*** | ***FF 50mcg (n=184)*** | ***FF 100mcg (n=184)*** | ***Placebo (n = 188)*** | ***FF 50mcg (n=185)*** | ***FF 100mcg (n=185)*** |
| ***Sex*** | | | | | | |
| Female | 78 (42%) | 80 (43%) | 73 (40%) | 81 (43%) | 84 (45%) | 83 (45%) |
| Male | 108 (58%) | 104 (57%) | 111 (60%) | 107 (57%) | 101 (55%) | 102 (55%) |
| ***Race*** | | | | | | |
| White | 148 (80%) | 156 (85%) | 140 (76%) | 141 (75%) | 136 (74%) | 131 (71%) |
| Black | 30 (16%) | 22 (12%) | 26 (14%) | 6 (3%) | 8 (4%) | 9 (5%) |
| Others | 8 (4%) | 6 (3%) | 18 (10%) | 41 (22%) | 41 (22%) | 45 (24%) |
| ***Age*** | | | | | | |
| **2 - <6** | **35 (19%)** | **32 (17%)** | **38 (21%)** | **38 (20%)** | **40 (22%)** | **42 (23%)** |
| 6 - <12 | 150 (81%) | 152 (83%) | 146 (79%) | 147 (78%) | 145 (78%) | 142 (77%) |
| 12+ | 1 | 0 | 0 | 3 | 0 | 1 |
| Mean (SD) | 8.0 (2.6) | 8.2 (2.4) | 8.0 (2.5) | 7.9 (2.5) | 7.7 (2.6) | 7.4 (2.5) |
| Median | 8.5 | 9.0 | 9.0 | 8.0 | 8.0 | 7.0 |
| **Range** | **2 - 12** | **2 - 11** | **2 - 11** | **3 - 12** | **2 - 11** | **2 - 12** |

| | | | | | | |
|---|---|---|---|---|---|---|
| ***Duration of SAR or PAR*** | | | | | | |
| 6 - < 1 year | 7 (4%) | 2 (1%) | 11 (6%) | 1 (<1%) | 4 (2%) | 3 (2%) |
| 1 to < 2 years | 25 (13%) | 22 (12%) | 28 (15%) | 23 (12%) | 22 (12%) | 22 (12%) |
| 2 to < 5 years | 94 (51%) | 85 (46%) | 74 (40%) | 101 (54%) | 99 (54%) | 104 (56%) |
| 5 to <10 years | 55 (30%) | 70 (38%) | 65 (36%) | 58 (31%) | 58 (31%) | 52 (28%) |
| 10+ years | 5 (3%) | 4 (2%) | 5 (3%) | 5 (3%) | 2 (1%) | 4 (2%) |
| ***Control Results (mm)*** | | | | | | |
| Mean (SD) | 0.25 (0.82) | 0.14 (0.57) | 0.21 (0.64) | 0.43 (1.1) | 0.58 (1.5) | 0.71 (1.9) |
| Median | 0 | 0 | 0 | 0 | 0 | 0 |
| **Range** | **0 - 7** | **0 - 4** | **0 - 4** | **0 - 6** | **0 - 10** | **0 - 20** |
| ***Histamine Results (mm)*** | | | | | | |
| Mean (SD) | 6.2 (4.0) | 6.6 (4.8) | 6.1 (4.0) | 5.7 (4.3) | 5.3 (3.2) | 5.4 (3.9) |
| Median | 5 | 5 | 5 | 5 | 5 | 4.8 |
| **Range** | **3 - 48** | **3 - 37** | **3 - 40** | **0 - 35** | **0 - 30** | **0 - 36** |
| ***AVG(AM,PM) Reflective TNSS*** | | | | | | |
| Mean (SD) | 8.4 (1.7) | 8.7 (1.8) | 8.6 (1.7) | 8.5 (1.6) | 8.5 (1.7) | 8.5 (1.6) |
| Median | 8.3 | 8.5 | 8.5 | 8.4 | 8.5 | 8.5 |
| **N, Range** | **186, 5.3-12** | **183, 6-12** | **184, 4.1-12** | **188, 5.8-12** | **185, 5.9-12** | **185. 5.7-12** |
| ***AM Instantaneous TNSS*** | | | | | | |
| Mean (SD) | 8.3 (2.0) | 8.4 (2.1) | 8.4 (1.8) | 8.2 (2.0) | 8.2 (2.1) | 8.2 (2.1) |
| Median | 8.3 | 8.5 | 8.3 | 8.3 | 8.3 | 8.3 |
| **N, Range** | **186, 0-12** | **183, 3-12** | **184, 3-12** | **188, 1.5-12** | **185, 1.8-12** | **185, 1.5-12** |

Data: DE.xpt; AT.xpt; RE.xpt; IN.xpt; Code: Demog.sas

### 3.1.3.3 Statistical Methodologies

Efficacy Variables

The primary efficacy variable was the mean change from baseline in daily rTNSS 2 weeks (PED01) or 4 weeks (PED02) treatment period. Key secondary efficacy measures were 1. Mean change from baseline over 2-weeks in AM pre-dose instantaneous TNSS (iTNSS) in subjects ages 6 to < 12 years; 2. Overall evaluation of response to therapy at endpoint in subjects ages 6 to < 12 years.

Multiple Comparisons

The multiple comparisons between each of the two active doses and placebo for the primary efficacy endpoint was performed in the following sequence to control the overall significance level of 0.05 on the primary efficacy endpoint:

- The comparison of FF 100mcg vs. placebo
- The comparison of FF 50mcg vs. placebo

No multiplicity adjustment was made on any secondary efficacy endpoints. Any p-values ≤0.05 was identified as nominally significant.

Sample Size

The planned sample size was based on the primary efficacy endpoint, the mean change from baseline in daily rTNSS over the entire treatment period in children ages 6 to <12 years. A total of 432 children ages 6 to <12 years would provide 90% power to detect a difference of 1.0 between active treatment and placebo using a two-sample t-test with a 0.05 two-sided significance level. A total of 576 subjects were required for this study, with 144 subjects ages 2 to <6 years and 432 subjects ages 6 to <12 years.

ITT
The intent-to-treat (ITT) population was defined as all randomized subjects who received at least one dose of study drug. The analysis of efficacy data was performed for subjects in the ITT population who are 6 to <12 years of age at randomization.

Missing Data Handling
The missing data handling was the same as for the adult study.

Primary Efficacy Analysis
The primary efficacy endpoint was the mean change from baseline over the 2 weeks (SAR) and 4 weeks (PAR) of the treatment period in daily rTNSS in subjects ages 6 to <12 years. The primary analysis method was the pairwise comparison of treatment groups (active vs. placebo) using analysis of covariance (ANCOVA), adjusting for baseline daily rTNSS, region (SAR only), country (PAR only), age, gender, and season (SAR only), in addition to treatment effect.

#### 3.1.2.2 Sponsor's Results and Conclusions

The sponsor concluded in proposed labeling (p11, SPL labeling.df) the following:

#### 3.1.2.3 Reviewer's Efficacy Analysis

**The sponsor's labeling claimed efficacy for children** aged 2 to < 12 years. According to the protocols and study reports, the pre-specified ITT population of interest is the children 6 to < 12 years. This reviewer did the primary analysis on three groups of populations (aged 6 to < 12 years, aged 2 to < 6 years, and aged 2 to < 12 years). The power calculations for SAR and PAR studies were based on subjects aged 6 to < 12 years.

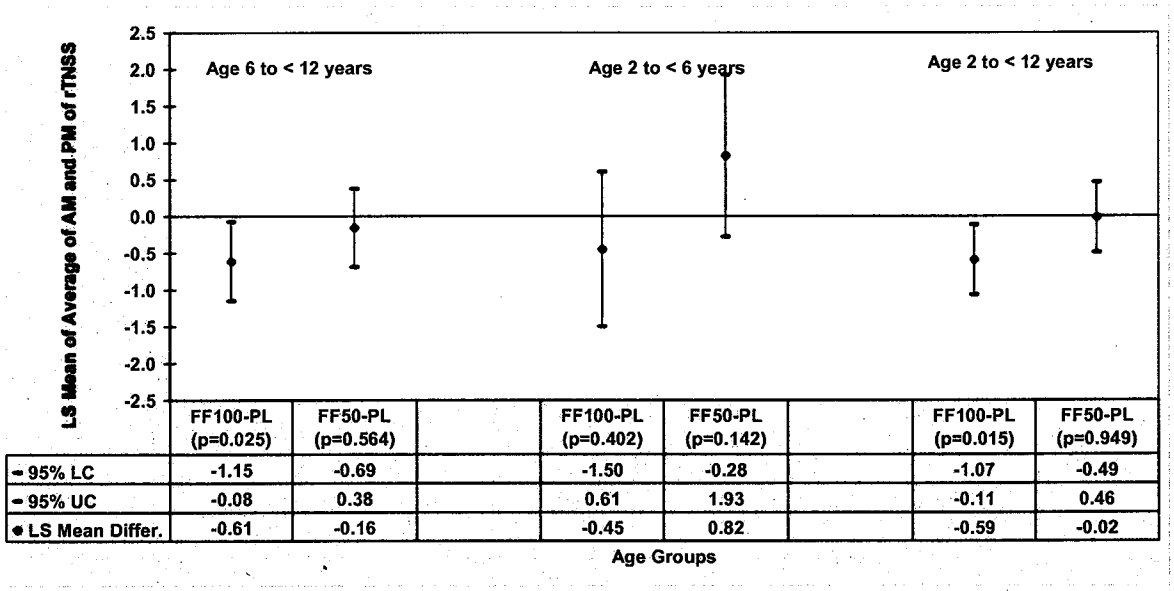
***Study PED01***
The primary analysis was based on ITT population which excluded two subjects aged 6 to < 12 years. One subject (subject 1123) in the placebo group was < 12 years of age at screening but at randomization was 12 years of age. One subject (subject 585) in the FF50mcg group was missing all baseline values for the diary data. Table 19 and
Figure **22** display the results of changes from baseline in daily rTNSS for the ITT population. The LS mean difference between FF 100mcg and placebo (-0.616) was statistically significant (p=0.025) in subjects aged 6 to < 12 years. The LS mean difference between FF 100mcg and

placebo (-0.45) was slightly smaller in subjects aged 2 to < 6 years. The LS mean difference between FF 50mcg and placebo did not reach the statistical significance (LS mean difference = -0.161, p=0.553) in subjects aged 6 to < 12 years; overall, FF 50mcg was not efficacious in children aged 2 to < 12 years.

Table 19. Analysis Results of daily rTNSS over 2-weeks for Study PED01

| *Treatment* | *Baseline* | *Change from Baseline* | | | |
|---|---|---|---|---|---|
| | *Mean (SD)* | *Mean (Sd)* | *LS Mean (SE)* | *FF – PL* | *p-value, 95% CI* |
| **Age 6 to < 12 years (Primary interesting ITT)** | | | | | |
| FF 100mcg (n=146) | 8.4 (1.1) | -3.1 (2.3) | -3.1 (0.21) | -0.61 | 0.025 (-1.15, -0.08) |
| FF 50mcg (n=151) | 8.5 (1.8) | -2.7 (2.5) | -2.7 (0.20) | -0.16 | 0.564 (-0.69, 0.38) |
| Placebo (n=149) | 8.3 (1.8) | -2.5 (2.4) | -2.5 (0.20) | | |
| **Age 2 to < 6 years** | | | | | |
| FF 100mcg (n=38) | 9.0 (1.6) | -3.7 (2.6) | -3.7 (0.39) | -0.45 | 0.402 (-1.50, 0.61) |
| FF 50mcg (n=32) | 8.8 (1.7) | -2.5 (1.9) | -2.4 (0.41) | 0.82 | 0.142 (-0.28, 1.93) |
| Placebo (n=35) | 8.5 (1.5) | -3.1 (2.1) | -3.3 (0.40) | | |
| **Age 2 to < 12 years** | | | | | |
| FF 100mcg (n=184) | 8.6 (1.7) | -3.2 (2.4) | -3.2 (0.18) | -0.59 | 0.015 (-1.07, -0.11) |
| FF 50mcg (n=183) | 8.7 (1.8) | -2.7 (2.4) | -2.6 (0.18) | -0.02 | 0.95 (-0.49, 0.46) |
| Placebo (n=184) | 8.4 (1.7) | -2.6 (2.4) | -2.6 (0.18) | | |

Figure 22. LS Mean Difference of Changes from Baseline in Primary Variable for Study PED01




| | FF100-PL (p=0.025) | FF50-PL (p=0.564) | | FF100-PL (p=0.402) | FF50-PL (p=0.142) | | FF100-PL (p=0.015) | FF50-PL (p=0.949) |
|---|---|---|---|---|---|---|---|---|
| - 95% LC | -1.15 | -0.69 | | -1.50 | -0.28 | | -1.07 | -0.49 |
| - 95% UC | -0.08 | 0.38 | | 0.61 | 1.93 | | -0.11 | 0.46 |
| • LS Mean Differ. | -0.61 | -0.16 | | -0.45 | 0.82 | | -0.59 | -0.02 |

*Study PED02*

**The sponsor's primary analysis was based on** the ITT population which excluded three subjects **aged 6 to 12 from Dr. Rooklin's site, one assigned to the FF 50mcg group and two assigned to** the FF 100mcg group. The result of a sensitivity analysis including those three subjects from Dr. **Rooklin's site was similar to the result of the primary analysis excluding those three subjects.** For FF100mcg, the reduction in daily rTNSS was numerically greater compared with placebo,

but the difference was not statistically significant (LS mean difference = -0.452, p=0.073). See Table 20 and
Figure **23** for details. The LS mean difference between FF100mcg and placebo (-0.53) was larger in the subjects aged 2 to < 6 years compared to the subjects aged 6 to < 12 years (-0.45) and the subjects aged 2 to < 12 years (-0.48).

Table 20. Analysis Results of Daily rTNSS over 4-weeks for Study PED02

| *Treatment* | *Baseline* | *Change from Baseline* | | | |
|---|---|---|---|---|---|
| | *Mean (SD)* | *Mean (SD)* | *LS Mean (SE)* | *FF – PL* | *p-value, 95% CI* |
| **Age 6 to < 12 years (Primary ITT)** | | | | | |
| FF 100mcg (n=140) | 8.6 (1.6) | -3.6 (2.4) | -3.9 (0.24) | -0.45 | 0.073 (-0.95, 0.04) |
| FF 50mcg (n=144) | 8.5 (1.6) | -3.8 (2.5) | -4.2 (0.24) | -0.75 | 0.003 (-1.24, -0.27) |
| Placebo (n=145) | 8.5 (1.5) | -3.0 (2.2) | -3.4 (0.24) | | |
| **Age 2 to < 6 years** | | | | | |
| FF 100mcg (n=39) | 8.1 (1.5) | -3.3 (2.0) | -3.8 (0.48) | -0.53 | 0.244 (-1.42, 0.37) |
| FF 50mcg (n=39) | 8.1 (1.8) | -3.9 (2.4) | -4.4 (0.51) | -1.1 | 0.015 (-1.99, -0.22) |
| Placebo (n=36) | 8.5 (1.8) | -3.0 (2.5) | -3.3 (0.52) | | |
| **Age 2 to < 12 years** | | | | | |
| FF 100mcg (n=179) | 8.5 (1.6) | -3.5 (2.4) | -3.8 (0.22) | -0.48 | 0.03 (-0.91, -0.05) |
| FF 50mcg (n=183) | 8.5 (1.7) | -3.8 (2.5) | -4.2 (0.22) | -0.82 | <0.01 (-1.25, -0.39) |
| Placebo (n=181) | 8.5 (1.6) | -3.0 (2.3) | -3.4 (0.22) | | |

Figure 23. LS Mean Difference of Changes from Baseline in Primary Variable for Study PED02

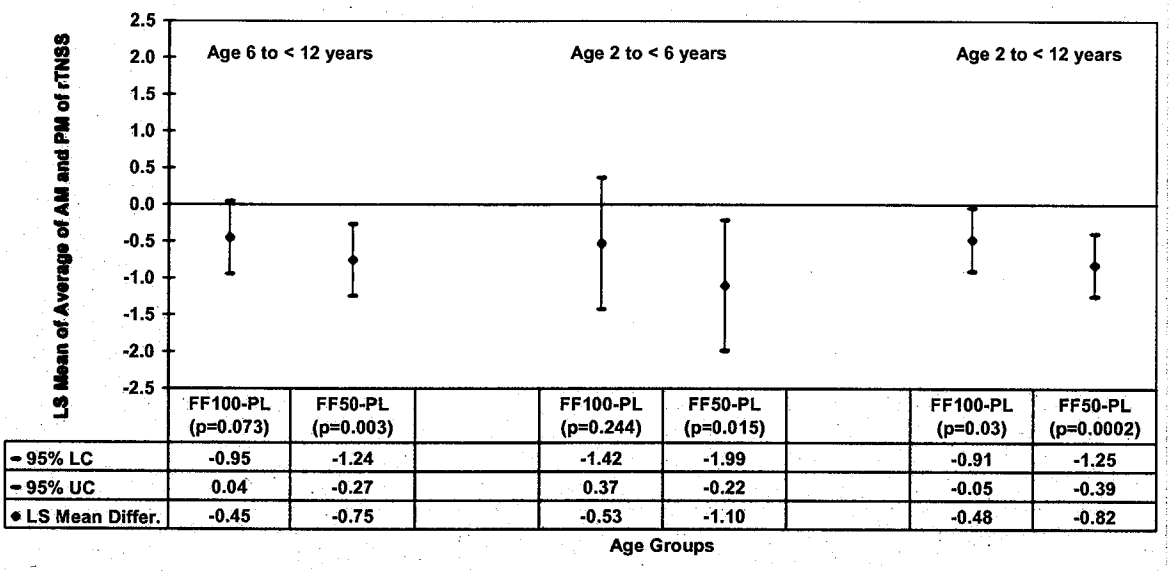



Table 21 displays the analysis results of AM pre-dose iTNSS over the study period for SAR and PAR studies. For FF100mcg, the reduction in daily iTNSS was statistically significantly greater compared with placebo in both studies (LS mean difference = -0.67, p=0.015 in PED01; LS mean difference = -0.65, p=0.009 in PED02).

Table 21. Analysis Results of AM Pre-dose of iTNSS over Study Period

| Treatment | Baseline | Change from Baseline | | | |
|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | LS Mean (SE) | FF – PL | p-value, 95% CI |
| **Age 6 to < 12 years (Primary ITT)** | | **SAR Study – PED01** | | | |
| FF 100mcg (n=146) | 8.3 (1.8) | -2.8 (2.3) | -2.8 (0.21) | -0.67 | 0.015 (-1.20, -0.13) |
| FF 50mcg (n=151) | 8.4 (2.1) | -2.4 (2.6) | -2.3 (0.20) | -0.23 | 0.397 (-0.76, 0.30) |
| Placebo (n=149) | 8.4 (2.0) | -2.2 (2.4) | -2.1 (0.20) | | |
| **Age 2 to < 6 years** | | | | | |
| FF 100mcg (n=38) | 8.6 (1.8) | -3.2 (2.5) | -3.1 (0.39) | -0.42 | 0.432 (-1.48, 0.64) |
| FF 50mcg (n=32) | 8.3 (2.2) | -1.9 (1.9) | -2.0 (0.41) | 0.75 | 0.180 (-0.36, 1.86) |
| Placebo (n=35) | 8.0 (1.8) | -2.6 (2.4) | -2.7 (0.40) | | |
| **Age 2 to < 12 years** | | | | | |
| FF 100mcg (n=184) | 8.4 (1.8) | -2.9 (2.3) | -2.8 (0.18) | -0.64 | 0.009 (-1.11, -0.16) |
| FF 50mcg (n=183) | 8.4 (2.1) | -2.3 (2.5) | -2.3 (0.18) | -0.07 | 0.773 (-0.55, 0.41) |
| Placebo (n=184) | 8.3 (2.0) | -2.2 (2.4) | -2.2 (0.18) | | |
| **Age 6 to < 12 years (Primary ITT)** | | **PAR Study – PED02** | | | |
| FF 100mcg (n=140) | 8.3 (2.0) | -3.2 (2.6) | -3.5 (0.23) | -0.65 | 0.009 (-1.14, -0.16) |
| FF 50mcg (n=144) | 8.3 (2.1) | -3.2 (2.8) | -3.6 (0.24) | -0.75 | 0.003 (-1.24, -0.27) |
| Placebo (n=145) | 8.3 (1.9) | -2.5 (2.1) | -2.9 (0.24) | | |
| **Age 2 to < 6 years** | | | | | |
| FF 100mcg (n=39) | 7.6 (2.3) | -2.6 (2.0) | -3.0 (0.45) | -0.46 | 0.286 (-1.30, 0.39) |
| FF 50mcg (n=39) | 7.6 (2.3) | -3.2 (2.5) | -3.5 (0.48) | -0.98 | 0.024 (-1.81, -0.13) |
| Placebo (n=36) | 8.0 (2.4) | -2.4 (2.5) | -2.6 (0.49) | | |
| **Age 2 to < 12 years** | | | | | |
| FF 100mcg (n=179) | 8.2 (2.1) | -3.1 (2.4) | -3.4 (0.21) | -0.61 | 0.005 (-1.04, -0.19) |
| FF 50mcg (n=183) | 8.2 (2.1) | -3.2 (2.7) | -3.6 (0.22) | -0.80 | 0.0002 (-1.22, -0.38) |
| Placebo (n=181) | 8.2 (2.0) | -2.4 (2.1) | -2.8 (0.22) | | |

Efficacy by Region or Country

The SAR study PED01 was conducted in 57 centers in US and was grouped by region (middle west, northeast, south center, south east, and west) and the PAR study PED02 was conducted in 61 centers in 6 countries, 36 centers out of 61 were in US. The interaction of treatment by region and treatment by country were not significant.

**Reviewer's Conclusion**

In children treated with Fluticasone Furoate nasal spray once daily, inconsistent results were observed across the SAR and PAR studies for the 50mcg and 100mcg doses. In SAR study (PED01), children aged 6 to <12 years treated with FF100mcg once daily exhibited statistically significant greater decreases in daily rTNSS than placebo-treated subjects; however, the superiority of FF50mcg over placebo did not reach statistical significance. In PAR study (PED02), children aged 6 to <12 years treated with FF100mcg once daily showed numerically reduced mean daily rTNSS compared with placebo but the difference was not statistically significant (p=0.07). For the FF50mcg dose the reductions in daily rTNSS were statistically significant compared with placebo. Note that on an important secondary variable, iTNSS, statistically significant treatment effects were observed for both doses in the PAR study.

## 3.2 Evaluation of Safety

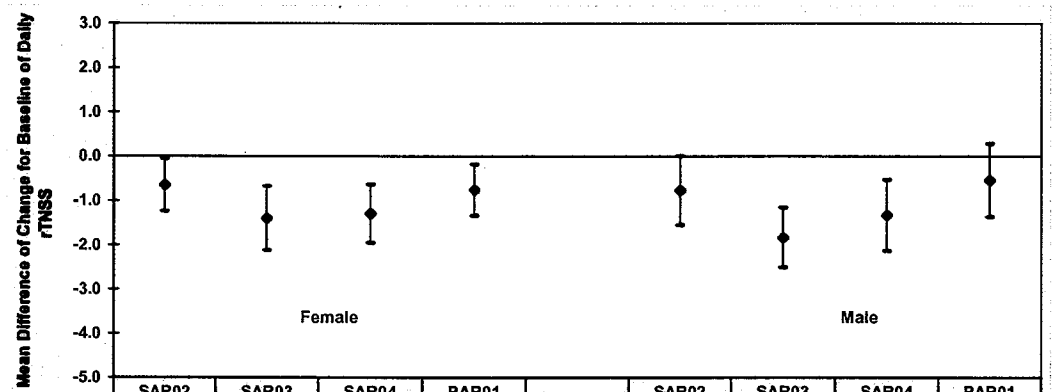
A detailed safety review can be found in the medical review.

# 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Gender, Race, Age, and Others

To explore consistency of the treatment effects across the levels of several predefined covariates, treatment-by-covariate interactions were evaluated for the primary efficacy endpoint. Figure 24, Figure 25, and Figure 26 display the results by age, gender, and race. The results by gender were highly consistent. There were too few patients to examine results for patients 65 and older. Statistically significant results are not expected in all subgroups due to the reduced sample size and natural variation expected when conducting multiple analyses.

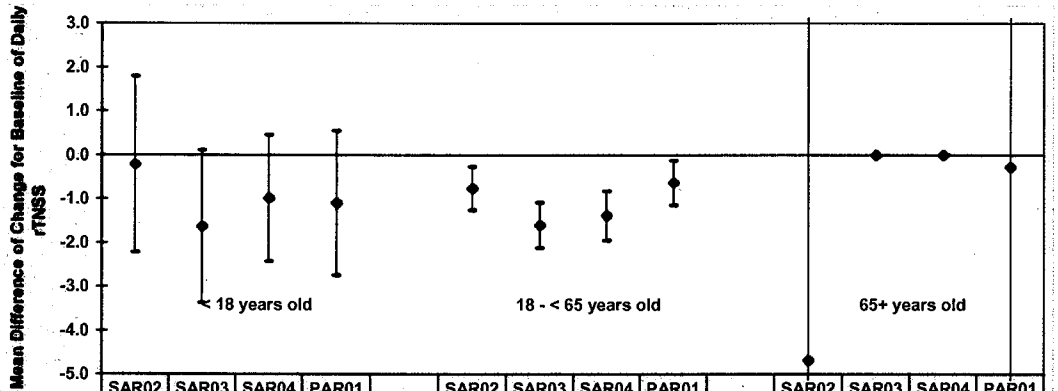
Figure 24. LS Mean and 95% CI of Change from Baseline of Daily rTNSS for Gender Group




| | SAR02 (n=191) | SAR03 (n=151) | SAR04 (n=180) | PAR01 (n=189) | | SAR02 (n=111) | SAR03 (n=132) | SAR04 (n=119) | PAR01 (n=113) |
|---|---|---|---|---|---|---|---|---|---|
| - 95%-LL | -1.24 | -2.12 | -1.96 | -1.33 | | -1.55 | -2.51 | -2.13 | -1.37 |
| - 95%-UL | -0.05 | -0.67 | -0.63 | -0.18 | | 0.01 | -1.16 | -0.53 | 0.29 |
| ◆ FF100 - PL | -0.65 | -1.40 | -1.30 | -0.76 | | -0.77 | -1.84 | -1.33 | -0.54 |

Sub-Groups (n=Patient Counts)

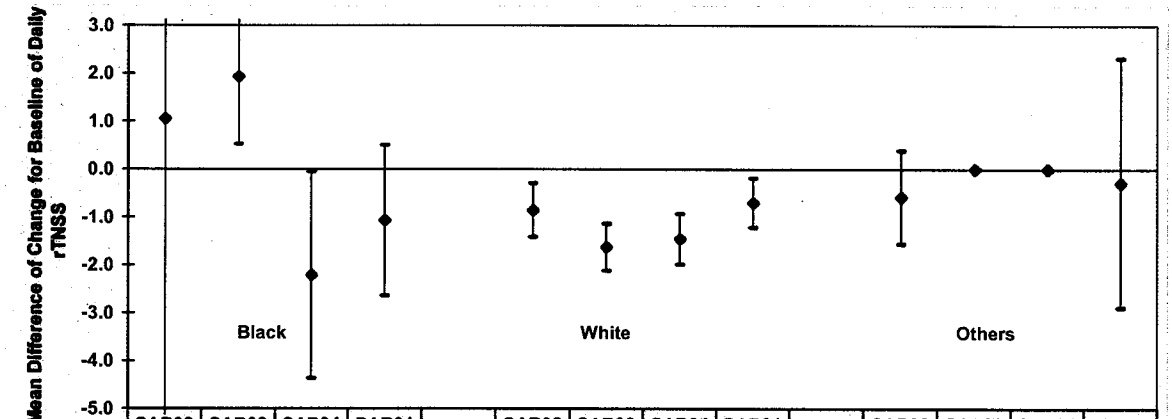
Figure 25. LS Mean and 95% CI of Change from Baseline of Daily rTNSS for Age Group




| | SAR02 (n=27) | SAR03 (n=25) | SAR04 (n=49) | PAR01 (n=32) | | SAR02 (n=265) | SAR03 (n=256) | SAR04 (n=247) | PAR01 (n=260) | | SAR02 (n=10) | SAR03 (n=2) | SAR04 (n=3) | PAR01 (n=10) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95%-LL | -2.22 | -3.38 | -2.43 | -2.75 | | -1.26 | -2.12 | -1.95 | -1.14 | | -17.92 | 0.00 | 0.00 | -5.15 |
| - 95%-UL | 1.79 | 0.10 | 0.45 | 0.54 | | -0.27 | -1.09 | -0.83 | -0.13 | | 8.55 | 0.00 | 0.00 | 4.59 |
| ◆ FF100 - PL | -0.21 | -1.64 | -0.99 | -1.10 | | -0.77 | -1.60 | -1.39 | -0.63 | | -4.68 | 0.00 | 0.00 | -0.28 |

Sub-Groups (n=Patient Counts)

Figure 26. LS Mean and 95% CI of Change from Baseline of Daily rTNSS for Race Group




| | SAR02 (n=12) | SAR03 (n=11) | SAR04 (n=26) | PAR01 (n=32) | | SAR02 (n=223) | SAR03 (n=269) | SAR04 (n=268) | PAR01 (n=253) | | SAR02 (n=67) | SAR03 (n=3) | SAR04 (n=5) | PAR01 (n=17) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - 95%-LL | -6.82 | 0.52 | -4.36 | -2.64 | | -1.42 | -2.12 | -1.99 | -1.22 | | -1.56 | 0.00 | 0.00 | -2.88 |
| - 95%-UL | 8.93 | 3.34 | -0.05 | 0.50 | | -0.29 | -1.14 | -0.93 | -0.19 | | 0.38 | 0.00 | 0.00 | 2.31 |
| ◆ FF100 - PL | 1.05 | 1.93 | -2.21 | -1.07 | | -0.86 | -1.63 | -1.46 | -0.70 | | -0.59 | 0.00 | 0.00 | -0.28 |

Sub-Groups (n=Patient Counts)

### 4.2 Other Special/Subgroup Populations

There are no other special/subgroup analyses.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

The following statistical issue was identified and resolved in the course of this review. The reader is referred to the specified section for details.

- Original RQLQ data sets were submitted with NDA submission on 28 June, 2006. On September 13, 2006, the sponsor re-submitted the corrected RQLQ data sets for three SAR studies and PAR study (See attachment 1 for details). The sponsor had taken the approach regarding RQLQ analysis in which the activity domain scores at endpoint were set as missing if text entries did not match 100% at baseline and final visit, resulting in a high percentage of missing values (26% - 52%) for the activity domain scores in the SAR and PAR studies. This reviewer found the problem and had a meeting with the sponsor on November, 2006. In light of this high proportion of missing data, this reviewer recommended to re-analyze the RQLQ data utilizing also the activity domain score where the text entries have the same meaning at baseline and endpoint even if they do not match 100% (e.g. walk, waling, gone walking, and taking a walk have different test string but have the same meaning) and asked the sponsor that if upon re-analysis the missing rate for a given study was still > 25%, a sensitivity analysis should be performed where

imputation should be employed for the missing activity scores at endpoint. The sponsor submitted the re-analysis of RQLQ and data on December 13, 2006. (See attachment 2 for details)

**Sponsor's Labeling**

**The sponsor's labeling was evaluated and the accuracy** of the statistical figures and tables was verified during this review; the statement proposed by the sponsor about onset of action in the **labeling was misleading.** ' '. According to the review, the onset of action was only observed in two out of four SAR studies at 8 hours after initial administration. In the other two studies, the onset of action was not seen until Hour 24.

### 5.2 Conclusions and Recommendations

The efficacy evaluation of four phase-III, randomized, multi-center, double-blind, parallel-group, and placebo-control studies (SAR02, SAR03, SAR04 and PAR01), demonstrated that Fluticasone Furoate Nasal Spray 27.5mcg is statistically significantly superior to placebo in improving the reflective Total Nasal Symptoms Score (rTNSS) after a dosage regimen of two sprays per nostril once daily (100mcg per day, hereafter referred to FF100mcg) in adult and adolescent patients 12 years and older with SAR or PAR. The efficacy evaluation of study SAR01, a phase-II, randomized, multi-center, double-blind, parallel-group, and placebo-control, and dose-finding study, demonstrated that all four dose regimens (50, 100, 200, 400mcg) of FF are statistically significantly superior to placebo in improving the Total Nasal Symptoms Score.

The efficacy of FF100mcg in treating for SAR subjects was supported by the key secondary endpoints of AM pre-dose instantaneous Total Nasal Symptoms Score (iTNSS), daily reflective Total Ocular Symptoms (rTOSS), overall evaluation of response to therapy, and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). For PAR subjects, the treatment difference between FF100mcg and placebo did not reach statistical significance for rTOSS and RQLQ.

The efficacy evaluation of study SAR05, the allergen challenge chamber (ACC) study, did not demonstrate significant onset of action. The onset of action was only observed in two out of four SAR studies at 8 hours after initial administration. In the other two studies, the onset of action was not seen until Hour 24. The improvement in AM pre-dose iTNSS was maintained over the full 24-hour dosing interval.

In children treated with Fluticasone Furoate nasal spray once daily, inconsistent results were observed between the SAR and PAR studies for the 50mcg and 100mcg doses. In SAR study (PED01), children aged 6 to <12 years treated with FF100mcg once daily exhibited statistically significant greater decreases in daily rTNSS than placebo-treated subjects; however, the superiority of FF50mcg over placebo did not reached the statistical significant. In PAR study (PED02), children aged 6 to <12 years treated with FF100mcg once daily showed numerically

reduced mean daily rTNSS compared with placebo but the difference was not statistically significant. For the FF50mcg dose the reductions in daily rTNSS were statistically significant compared with placebo.

To explore consistency of the treatment effects across the levels of several predefined covariates (age, gender, and race), treatment-by-covariate interactions were evaluated for the primary efficacy endpoint. The results by gender were highly consistent. There were too few patients to examine results for patients 65 and older. Statistically significant results are not expected in all subgroups due to the reduced sample size and natural variation expected when conducting multiple analyses.

EOF

# 6. Attachments

## 6.1 Attachment Sponsor's Data Revisions for RQLQ


September 13, 2006

Badrul A. Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

**GlaxoSmithKline**
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709
Tel. 919 483 2100
www.gsk.com

**Re: NDA 22-051; Fluticasone Furoate Nasal Spray**
**Amendment to Pending Application: Other; Reanalyzed Health Outcome Data**

Dear Dr. Chowdhury:

A data discrepancy issue regarding the "Activities Domain" of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) has been noted in the RQLQ data included in the original NDA 22-051 submitted June 28, 2006. This data discrepancy was discovered during the preparation of the statistical package for the recently completed second perennial allergic rhinitis study (FFR106080) which was reported in the NDA as an "ongoing study". For the RQLQ used in all efficacy studies for this project and included in the NDA (FFR20001, FFR30003, FFR103184, FFR104861, and FFR30002), subjects were instructed to identify the three most important activities in which they have been limited by the nose/eye symptoms during the last week. This information was captured at baseline and the same activities and wording of those activities were subsequently transcribed onto the endpoint/early withdrawal questionnaire. However, approximately 24-52% of subjects across all studies had non-matching text entered for the "Activities Domain" at baseline and the end of the study (e.g., similar meanings with different text strings or different activities all together), and, thus, the change from baseline in this domain cannot be determined in these individuals. This information was handled appropriately in creating the analysis dataset for the phase 2b study, FFR20001, but not in the phase 3 studies (FFR30003, FFR103184, FFR104861, and FFR30002).

The non-matching incidence appeared to occur randomly across treatment groups within each of these four studies. In addition, the reanalysis results (with the corrected data) showed that the overall conclusion on RQLQ (both on statistical tests and clinical interpretation based on minimally important difference [MID]) remained the same for these studies; however, the numerical results were slightly different for the "Activities Domain" and for the overall RQLQ score.

An additional data issue was uncovered during the revision validation for FFR103184, the visitnum (numerical field used to identify the visit and to merge with other datasets) for the early withdrawal visit in RQLQ was set as equal to 50, which was different from the rest of the CRF data where visitnum=120 for early withdrawal. This issue resulted in the accidental exclusion of subjects who withdrew from the study but were on treatment for at least 7 days and had RQLQ assessments, and, thus, should have been used in the endpoint calculation due to data merging. The revisions did impact the numerical results of all 7 domains and overall RQLQ score in this study, but did not change the overall conclusion on RQLQ assessment nor the clinical interpretation based on MID with the exception of the Eye-symptoms domain.

In order to correct the above noted data issues related to RQLQ the following documents have been revised accordingly and the addenda are provided in this submission:

1. FFR30003, FFR103184, FFR104861, and FFR30002: Clinical Study Report (CSR) amendments revising Health Outcomes Section to reflect the corrected RQLQ analysis data.

2. FFR30003, FFR103184, FFR104861, and FFR30002: RQLQ related SAS dataset, along with define.pdf file, raw data from CRF (rqlq) and analysis-ready data (rqlq_anl).

3. Revised Health Outcomes Section in the Summary of Clinical Efficacy (Module 2.7.3), Clinical Overview (Module 2.5) and Integrated Summary of Efficacy (ISE; Module 5.3.5.3). For ISE, the RQLQ analysis-ready SAS dataset is also provided.

4. Revised labeling incorporating the new numbers for RQLQ data.

The above revised information on RQLQ is provided for completeness and accuracy purposes and does not result in a change in the overall conclusion for RQLQ outcome as provided in the original NDA 22-051 submission.

This submission is provided in electronic format. Please see the attached Guide to Reviewer for complete details regarding this electronic submission. If you have any questions regarding this submission, please contact me at (919) 483-9318.

Sincerely,

Munir Abdullah

Munir Abdullah, Ph.D.
Director
Regulatory Affairs

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

6.2 Attachment Sponsor's Reanalysis of RQLQ

December 13, 2006

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3
Tel. 919 483 2100
www.gsk.com

Badrul A. Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

**Re: NDA 22-051; Fluticasone Furoate Nasal Spray**
**Response to FDA Request/Comment: Other; Reanalyzed Health Outcome Data**

Dear Dr. Chowdhury:

Reference is made to your fax dated November 17, 2006, and the teleconference held on November 20, 2006, where FDA statisticians informed GlaxoSmithKline (GSK) that the approach taken in the analysis of RQLQ data for Phase 3 clinical studies (FFR30003, FFR104861, FFR103184, and FFR30002) in NDA 22-051 where the activity domain scores at endpoint were set as missing if texts entries did not match 100% at baseline and final visit, resulting in a high percentage of missing values (26% to 52%) for the activity domain scores in the clinical studies was not acceptable. In light of this high proportion of missing data, FDA recommended to re-analyze the RQLQ data utilizing also the activity domain scores where the text entries have the same meaning at baseline and endpoint even if they do not match 100% (e.g. walk, walking, gone walking, and taking a walk have different text string but have the same meaning).

FDA further asked GSK that if upon re-analysis the missing rate for a given study was still > 25%, a sensitivity analysis should be performed where imputation should be employed for the missing activity scores at endpoint. The prorating method based on the other non-missing activity scores specified in the RAP for the overall score can be used as an imputation method.

In this submission GSK is providing the re-analyzed activity domain scores for RQLQ analysis in the three SAR studies (FFR30003, FFR104861, and FFR103184) and one PAR study (FFR30002) in accordance with the request and agreement with the FDA reviewers at the teleconference held on November 20, 2006.

This submission is provided in electronic format. Please see the attached Guide to Reviewer for complete details regarding this electronic submission. If you have any questions regarding this submission, please contact me at (919) 483-9318.

Sincerely,

Munir Abdullah

Munir Abdullah, Ph.D.
Director
Regulatory Affairs

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

# 1. INTRODUCTION

This document provides the information requested by FDA in a teleconference held on November 20, 2006. FDA statisticians had requested GlaxoSmithKline (GSK) to conduct the re-analysis for the activity domain scores for RQLQ analysis in the three SAR studies (FFR30003, FFR104861, and FFR103184) and one PAR study (FFR30002) and provide this reanalyzed data to NDA 22-051.

In the fluticasone furoate nasal spray NDA 22-051, GSK had taken the approach regarding RQLQ analysis where the activity domain scores at endpoint were set as missing if texts entries did not match 100% at baseline and final visit, resulting in a high percentage of missing values (26% to 52%) for the activity domain scores in the clinical studies. In light of this high proportion of missing data, FDA recommended to re-analyze the RQLQ data utilizing also the activity domain scores where the text entries have the same meaning at baseline and endpoint even if they do not match 100% (e.g. walk, walking, gone walking, and taking a walk have different text string but have the same meaning).

FDA further asked GSK that if upon re-analysis the missing rate for a given study was still > 25%, a sensitivity analysis should be performed where imputation should be employed for the missing activity scores at endpoint. The prorating method based on the other non-missing activity scores specified in the RAP for the overall score can be used as an imputation method.

# 2. ANALYSIS DATASET AND RESULT OUTPUT

For each study, three datasets are provided, as outlined in Table 1 below.

Dataset (allnmact) was created by subsetting out the activity domain data for subjects who did not have perfect matches at baseline and endpoint on the text entries for all 3 activities. A variable (Match) was manually assigned to either Yes, if the meanings were the same from baseline to endpoint for the activity (e.g., 'walk' at baseline and 'walking' at endpoint was considered as a matching pair and was utilized in the analyses provided in this document); or No, if the meanings were different (e.g., 'walk' at baseline and 'watching TV' at endpoint was considered as a non-matching pair, and the endpoint corresponding to 'walk' assessed at baseline was set as missing, and was imputed in the sensitivity analyses as specified in the later Section). Minor spelling errors were ignored. Abbreviations or short-hands (e.g 'at' vs. @), 'activities' vs. 'Act.') were allowed. If subjects entered the number, instead of the text, of an example given in the RQLQ instructions for the activities domain in the CRF (see Section 7), the corresponding activities were also used for matching purposes.

There were also subjects who had the matching activities at baseline and at endpoint, but the actual scores were missing either at baseline or at endpoint. The above two examples accounted for most of the subjects that were not included in the analysis for the activity

domain of RQLQ which was previously submitted to NDA 22-051 in an amendment dated September 13, 2006.

The modified dataset (rqlq_mod) was created by merging the dataset 'allnmact' with the original 'rqlq' data set and adjusting the activities text for those records where the variable match='Y'.

The analysis dataset (rqlq_anal) contains the overall and individual domain scores at baseline, at endpoint, and change from baseline, derived based on the 'rqlq_mod' using the same derivation method as in creating the analysis dataset in the amendment to NDA 22-051 dated September 13, 2006. For each study re-analyzed (FFR30003, FFR104861, FFR103184, and FFR30002), three different analyses were conducted based on the dataset 'rqlq_anl', as specified in Table 1 below:

**Table 1 Data Sets and Output Tables**

| | Description | Name of Dataset or Output Name / Table # | Variable identifier for overall and activity scores |
|---|---|---|---|
| Dataset | Subjects with non-matching activities, including those considered matching in meaning and those truly non-matching | allnmact | |
| | Modified RQLQ dataset, where activities from baseline to endpoint with same meanings are considered as matching activities. | rqlq_mod | |
| | Derived RQLQ analysis dataset. | rqlq_anl | |
| Analysis Output | Summary of Missing Date due to Missing Scores and/or Non-matching Activities | T_miss_nomtch_summ Table 1 | |
| | Summary of RQLQ Scores Based on the Modified RQLQ dataset without Imputation on Missing Activity Scores[1] | t_rqlq_sum_macts Table 2 | Domaincd= 0 & 1, respectively |
| | Analysis of Mean Change from Baseline to Endpoint in RQLQ Scores Based on the Modified RQLQ dataset without Imputation on Missing Activity Scores[1] | t_rqlq_anl_macts Table 3 | |
| | Summary of RQLQ Scores Based on the Modified RQLQ Dataset – Imputing Missing Scores if There were at Least Two Non-missing Activity Scores[2] | t_rqlq_sum_sens1 Table 4 | Domaincd= 0.1 & 1.1, respectively |
| | Sensitivity Analysis #1 of Mean Change from Baseline to Endpoint in RQLQ Scores Based on the Modified RQLQ Dataset – Imputing Missing Scores if There Were at Least Two Non-missing Activity Scores[2] | t_rqlq_anl_sens1 Table 5 | |
| | Summary of RQLQ Scores based on the Modified RQLQ Dataset – Imputing Missing Scores if There Was at Least One Non Activity Score[3] | t_rqlq_sum_sens2 Table 6 | Domaincd= 0.2 & 1.2, respectively |
| | Sensitivity Analysis #2 of Mean Change from Baseline to Endpoint in RQLQ Scores based on the Modified RQLQ Dataset – Imputing Missing Scores if There Was at Least One Non Activity Score[3] | t_rqlq_anl_sens2 Table 7 | |

1. Re-analysis without any imputation on missing values for the activity domain either due to missing scores or non-matching activities. Subjects with three matching activities (at least 75%) and non-missing scores are included in this analysis.

2. Sensitivity analysis with imputation for the endpoint result, using the pro-rating method specified in the RAP, for subjects with at least two matching activities at baseline and at endpoint with non-missing activity scores.
3. Sensitivity analysis with imputation for the endpoint result, using the pro-rating method specified in the RAP, for subjects with at least one matching activity at baseline and at endpoint with non-missing activity scores.

These reanalyses and sensitivity analyses only involved the modification of the data on the activity domain and the overall RQLQ scores, and thus only impacted the results for these parameters. All other six individual domain results remain unchanged.

# 3. MISSING DATA IN ACTIVITY DOMAIN

For each study, the dataset that includes subjects with missing scores (denoted as Set A) were merged with the dataset that includes subjects with non-matching activities (i.e. of different meanings at baseline and at endpoint, denoted as Set B). Subjects with missing data in activity domain either due to non-matching text entries or missing scores were summarized in Table 2 below, using three mutually exclusive sets (A but not B, B but no A, A and B).

**Table 2 Summary of Missing Data in Activity Domain.**

| Protocol | Reason for Missing | Placebo | FF 110mcg | Total |
|---|---|---|---|---|
| FFR30003 | Subjects only had missing scores | 17 (11%) | 16 (11%) | 33 (11%) |
| | Subjects only had non-matching activities from baseline to endpoint | 0 | 0 | 0 |
| | Subjects had both non-matching activities and missing scores | 0 | 1 (<1%) | 1 (<1%) |
| | Total | 17 (11%) | 17 (11%) | 34 (11%) |
| FFR104861 | Subjects only had missing scores | 18 (12%) | 21 (14%) | 39 (13%) |
| | Subjects only had non-matching activities from baseline to endpoint | 11 ( 7%) | 14 ( 9%) | 25 ( 8%) |
| | Subjects had both non-matching activities and missing scores | 2 (1%) | 4 (3%) | 6 ( 2%) |
| | Total | 31 (21%) | 39 (26%) | 70 (23%) |
| FFR103184 | Subjects only had missing scores | 7 ( 5%) | 10 ( 7%) | 17 ( 6%) |
| | Subjects only had non-matching activities from baseline to endpoint | 34 (24%) | 33 (23%) | 67 (24%) |
| | Subjects had both non-matching activities and missing scores | 7 ( 5%) | 7 ( 5%) | 14 ( 5%) |
| | Total | 48 (33%) | 50 (35%) | 98 (34%) |
| FFR30002 | Subjects only had missing scores | 15 (10%) | 13 ( 9%) | 28 ( 9%) |
| | Subjects only had non-matching activities from baseline to endpoint | 8 (5%) | 10 ( 7%) | 18 ( 6%) |
| | Subjects had both non-matching activities and missing scores | 1 (<1%) | 5 ( 3%) | 6 ( 2%) |
| | Total | 24 (16%) | 28 (19%) | 52 (17%) |

# 4. RE-ANALYSIS RESULTS

Re-analysis results utilizing all scores from activities with same meanings at baseline a endpoint, without any imputation, are summarized here.

**Table 3 Re-analysis results for the overall score and activity domain of RQLQ**

| | | Placebo | FF 110mcg |
|---|---|---|---|
| **FFR30003** | N | 150 | 152 |
| **Overall** | n | 149 | 149 |
| | LS Mean Change (SE) | -0.97 (0.14) | -1.66 (0.14) |
| | LS Mean Difference (p-value) | | -0.690 (<0.001) |
| | 95% CI | | (-1.08, -0.30) |
| | | | |
| **Activities** | n | 133 | 135 |
| | LS Mean Change (SE) | -1.01 (0.17) | -1.73 (0.17) |
| | LS Mean Difference (p-value) | | -0.720 (0.003) |
| | 95% CI | | (-1.19, -0.25) |
| | | | |
| **FFR104861** | N | 148 | 151 |
| **Overall** | n | 144 | 144 |
| | LS Mean Change (SE) | -1.16 (0.12) | -1.77 (0.11) |
| | LS Mean Difference (p-value) | | -0.604 (<0.001) |
| | 95% CI | | (-0.93, -0.28) |
| | | | |
| **Activities** | n | 117 | 112 |
| | LS Mean Change (SE) | -1.25 (0.15) | -1.96 (0.15) |
| | LS Mean Difference (p-value) | | -0.718 (<0.001) |
| | 95% CI | | (-1.09, -0.35) |
| | | | |
| **FFR103184** | N | 144 | 141 |
| **Overall** | n | 140 | 137 |
| | LS Mean Change (SE) | -1.53 (0.10) | -2.23 (0.11) |
| | LS Mean Difference (p-value) | | -0.701 (<0.001) |
| | 95% CI | | (-0.99, -0.41) |
| | | | |
| **Activities** | n | 96 | 91 |
| | LS Mean Change (SE) | -1.79 (0.16) | -2.68 (0.17) |
| | LS Mean Difference (p-value) | | -0.894 (<0.001) |
| | 95% CI | | (-1.35, -0.44) |
| | | | |
| **FFR30002** | N | 153 | 149 |
| **Overall** | n | 151 | 143 |
| | LS Mean Change (SE) | -1.18 (0.13) | -1.41 (0.13) |
| | LS Mean Difference (p-value) | | -0.227 (0.214) |
| | 95% CI | | (-0.59, 0.13) |
| | | | |
| **Activities** | n | 127 | 119 |
| | LS Mean Change (SE) | -1.30 (0.18) | -1.31 (0.17) |
| | LS Mean Difference (p-value) | | -0.012 (0.960) |
| | 95% CI | | (-0.50, 0.48) |

# 5. SENSITIVITY ANALYSIS

Two sensitivity analyses, imputing missing activity scores based on the pro-rating method, were performed for each study regardless of the percentage of missing data for the activity domain of RQLQ. The results are summarized in Table 4 below.

**Table 4 Sensitivity analysis results for the overall score and activity domain of RQLQ**

| | | Sensitivity Analysis #1[†] | | Sensitivity Analysis #2[¶] | |
|---|---|---|---|---|---|
| | | **Placebo** | **FF 110mcg** | **Placebo** | **FF 110mcg** |
| **FFR30003** | N | 150 | 152 | 150 | 152 |
| **Overall** | n | 149 | 149 | 149 | 149 |
| | LS Mean Change (SE) | -0.97 (0.14) | -1.66 (0.14) | -0.97 (0.14) | -1.66 (0.14) |
| | LS Mean Difference (p-value) | -0.689 (<0.001) | | -0.689 (<0.001) | |
| | 95% CI | (-1.08, -0.30) | | (-1.08, -0.30) | |
| **Activities** | n | 137 | 140 | 138 | 140 |
| | LS Mean Change (SE) | -1.01 (0.16) | -1.66 (0.17) | -0.99 (0.16) | -1.66 (0.17) |
| | LS Mean Difference (p-value) | -0.649 (0.006) | | -0.670 (0.005) | |
| | 95% CI | (-1.11, -0.19) | | (-1.13, -0.21) | |
| | | | | | |
| **FFR104861** | N | 148 | 151 | 148 | 151 |
| **Overall** | n | 144 | 144 | 144 | 144 |
| | LS Mean Change (SE) | -1.16 (0.12) | -1.77 (0.11) | -1.16 (0.12) | -1.77 (0.11) |
| | LS Mean Difference (p-value) | -0.604 (<0.001) | | -0.610 (<0.001) | |
| | 95% CI | (-0.93, -0.28) | | (-0.94, -0.28) | |
| **Activities** | n | 125 | 128 | 133 | 130 |
| | LS Mean Change (SE) | -1.24 (0.14) | -2.01 (0.14) | -1.22 (0.15) | -2.02 (0.15) |
| | LS Mean Difference (p-value) | -0.768 (<0.001) | | -0.798 (<0.001) | |
| | 95% CI | (-1.13, -0.41) | | (-1.17, -0.43) | |
| | | | | | |
| **FFR103184** | N | 144 | 141 | 144 | 141 |
| **Overall** | n | 140 | 137 | 140 | 137 |
| | LS Mean Change (SE) | -1.53 (0.10) | -2.23 (0.11) | -1.53 (0.10) | -2.23 (0.11) |
| | LS Mean Difference (p-value) | -0.702 (<0.001) | | -0.697 (<0.001) | |
| | 95% CI | (-0.99, -0.41) | | (-0.99, -0.41) | |
| **Activities** | n | 113 | 111 | 126 | 120 |
| | LS Mean Change (SE) | -1.82 (0.14) | -2.72 (0.14) | -1.85 (0.13) | -2.70 (0.14) |
| | LS Mean Difference (p-value) | -0.900 (<0.001) | | -0.850 (<0.001) | |
| | 95% CI | (-1.30, -0.50) | | (-1.23, -0.47) | |
| | | | | | |

**Table 4 (cont) Sensitivity analysis results for the overall score and activity domain of RQLQ**

| | | Sensitivity Analysis #1† | | Sensitivity Analysis #2¶ | |
|---|---|---|---|---|---|
| | | Placebo | FF 110mcg | Placebo | FF 110mcg |
| FFR30002 | N | 153 | 149 | 153 | 149 |
| Overall | n | 151 | 143 | 151 | 143 |
| | LS Mean Change (SE) | -1.18 (0.13) | -1.41 (0.13) | -1.17 (0.13) | -1.41 (0.13) |
| | LS Mean Difference (p-value) | -0.227 (0.214) | | -0.234 (0.200) | |
| | 95% CI | (-0.59, 0.13) | | (-0.59, 0.12) | |
| Activities | n | 134 | 125 | 137 | 130 |
| | LS Mean Change (SE) | -1.35 (0.18) | -1.38 (0.17) | -1.22 (0.17) | -1.38 (0.17) |
| | LS Mean Difference (p-value) | -0.026 (0.917) | | -0.158 (0.517) | |
| | 95% CI | (-0.51, 0.46) | | (-0.64, 0.32) | |

†: Pro-rate if at least two matching activities for baseline and endpoint with non-missing scores.
¶: Pro-rate if at least one matching activity for baseline and endpoint with non-missing scores.

# 6. SUMMARY OF RQLQ ANALYSES

The percentage of subjects used for the re-analysis of activity domain were similar for both treatment groups across studies, ranged from 66% - 89% in the re-analysis without imputation, 79% - 92% in the sensitivity analysis #1, and 86 - 92% in the sensitivity analysis #2, as summarized in Table 5 below. Missing data in the activity domain appeared to occur at random across treatment groups within each study, regardless of the reason for missing (i.e., either due to non-matching activities from baseline to endpoint or actual missing scores).

**Table 5 Number (percentage) of Subjects Included in the Analysis for the Activity Domain of RQLQ.**

| Protocol ID | | Placebo | FF 110mcg | Total |
|---|---|---|---|---|
| FFR30003 | N | 150 | 152 | 302 |
| | Re-Analysis | 133 (89%) | 135 (89%) | 268 (89%) |
| | Sensitivity Analysis #1 | 137 (91%) | 140 (92%) | 277 (92%) |
| | Sensitivity Analysis #2 | 138 (92%) | 140 (92%) | 278 (92%) |
| | | | | |
| FFR104861 | N | 148 | 151 | 299 |
| | Re-Analysis | 117 (79%) | 112 (74%) | 229 (77%) |
| | Sensitivity Analysis #1 | 125 (84%) | 128 (85%) | 253 (85%) |
| | Sensitivity Analysis #2 | 133 (90%) | 130 (86%) | 263 (88%) |
| | | | | |
| FFR103184 | N | 144 | 141 | 285 |
| | Re-Analysis | 96 (67%) | 91 (65%) | 187 (66%) |
| | Sensitivity Analysis #1 | 113 (78%) | 111 (79%) | 224 (79%) |
| | Sensitivity Analysis #2 | 126 (88%) | 120 (85%) | 246 (86%) |
| | | | | |
| FFR30002 | N | 153 | 149 | 302 |
| | Re-Analysis | 127 (83%) | 119 (80%) | 246 (81%) |
| | Sensitivity Analysis #1 | 134 (88%) | 125 (84%) | 259 (86%) |
| | Sensitivity Analysis #2 | 137 (90%) | 130 (87%) | 267 (88%) |

The estimated treatment effect from re-analysis and sensitivity analyses was compared to the results provided in NDA 22-051 amendment dated September 13, 2006, and summarized in Table 6 below.

For the overall RQLQ score, missing data on the activity domain did not have any material impact on the analysis results, regardless of imputation on missing data or the imputation methods. For each study, all three analyses performed for the overall RQLQ score in this document and the analysis conducted and submitted previously to NDA 22-051 amendment dated September 13, 2006, utilized more than 95% of the subject data, provided the estimated treatment effects (based on the LS mean) that were differed by $< 0.01$ of each other, and did not change the overall conclusion of the statistical analysis nor the clinical interpretation based on MID, regardless of the analysis method.

For the activity domain score, the numerical result differed depending on the analysis method, but the overall conclusion of the statistical analysis and the clinical interpretation based on MID remained the same for each study.

**Table 6 Summary of Analysis Results for the Overall Score and the Activity Domain of RQLQ**

| | Analysis in NDA Amendment § | | Re-Analysis * | | Sensitivity Analysis #1 † | | Sensitivity Analysis #2 † | |
|---|---|---|---|---|---|---|---|---|
| | LSDiff | p-value | LSDiff | p-value | LSDiff | p-value | LSDiff | p-value |
| FFR30003 | | | | | | | | |
| Overall | -0.688 | <0.001 | -0.690 | <0.001 | -0.689 | <0.001 | -0.689 | <0.001 |
| Activities | -0.644 | 0.034 | -0.720 | 0.003 | -0.649 | 0.006 | -0.670 | 0.005 |
| | | | | | | | | |
| FFR104861 | | | | | | | | |
| Overall | -0.599 | <0.001 | -0.604 | <0.001 | -0.604 | <0.001 | -0.610 | <0.001 |
| Activities | -0.588 | 0.027 | -0.718 | <0.001 | -0.768 | <0.001 | -0.798 | <0.001 |
| | | | | | | | | |
| FFR103184 | | | | | | | | |
| Overall | -0.700 | <0.001 | -0.701 | <0.001 | -0.702 | <0.001 | -0.697 | <0.001 |
| Activities | -0.902 | <0.001 | -0.894 | <0.001 | -0.900 | <0.001 | -0.850 | <0.001 |
| | | | | | | | | |
| FFR30002 | | | | | | | | |
| Overall | -0.226 | 0.215 | -0.227 | 0.214 | -0.227 | 0.214 | -0.234 | 0.200 |
| Activities | 0.021 | 0.953 | -0.012 | 0.960 | -0.026 | 0.917 | -0.158 | 0.517 |
| | | | | | | | | |

*: based on Table 3 above.

†: based on Table 4 above.

§: NDA 22-051 amendment dated September 13, 2006 providing re-analyzed Health Outcomes Data.

EOF

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
---
Feng Zhou
2/21/2007 07:59:40 AM
BIOMETRICS

Joy Mele
2/23/2007 03:25:00 PM
BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

# Statistical Review and Evaluation

## CLINICAL STUDIES

| | |
|---|---|
| NDA/Serial Number: | N22-051 |
| Drug Name: | Fluticasone Furoate Nasal Spray 27.5mcg |
| Indication(s): | Proposed Indication: SAR, PAR in adults and children ages 2 year and older |
| Applicant: | The GlaxoSmithKline group of companies |
| Date(s): | Received 6/28/06; User Fee 4/28/07 |
| Review Priority: | Standard |
| | |
| Biometrics Division: | Division of Biometrics II (HFD-715) |
| Statistical Reviewer: | Feng Zhou, Statistical Reviewer |
| Concurring Reviewers: | Ruthanna C Davi, (Biometrics Team Leader) |
| | |
| Medical Division: | Division of Pulmonary and Allergy Drug Products (HFD-570) |
| Clinical Team: | Anthony Durmowicz, M.D. (Medical Reviewer)<br>Badrul A Chowdhury, M.D. (Medical Division Director) |
| Project Manager: | Ladan Jafari (HFD-570) |

Keywords: Clinical Studies, NDA review, Dropouts

## FILING CHECKLIST

| Item | Check (NA if not applicable) |
|---|---|
| Index sufficient to locate necessary reports, tables, etc. | Yes |
| Original protocols & subsequent amendments available in the NDA | Yes |
| Safety and efficacy for gender, racial, and geriatric subgroups investigated | Yes |
| Data sets in EDR conform to applicable guidances. | Yes |

The submission is filable from a statistical perspective.

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
---
Feng Zhou
8/23/2006 09:03:07 AM
BIOMETRICS

Ruth Davi
8/23/2006 09:55:50 AM
BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

| | |
|---|---|
| **NDA Number:** | 22,051 / Serial 000 |
| **Drug Name:** | TRADENAME™ (Fluticasone Furoate Nasal Spray) |
| **Indication(s):** | Treatment for the symptoms of seasonal and perennial rhinitis in adults and children aged 2 years and older. |
| **Applicant:** | Glaxo Smith Kline |
| **Date(s):** | Submitted 06/28/06 |
| **Review Priority:** | Standard |
| | |
| **Biometrics Division:** | Division 6, HFD-705 |
| **Statistical Reviewer:** | Steve Thomson, HFD-705 |
| **Concurring Reviewer:** | Team Leader: Karl Lin, Ph. D., HFD-705 |
| **Medical Division:** | Pulmonary and Allergy Drug Products, HFD-570 |
| **Toxicologist:** | Reviewer: Huiqing Hao, Ph.D., HFD-570<br>Team Leader: Timothy McGovern, Ph.D., HFD-570 |
| **Project Manager:** | Ladan Jafari, HFD-570 |
| | |
| **Keywords:** | Carcinogenicity, Cox regression, Kaplan-Meier product limit, Survival analysis, Trend test |

# Table of Contents

# 1. EXECUTIVE SUMMARY

This submission was intended to assess the carcinogenic potential of fluticasone fumarate when administered daily by inhalation for two years to mice and rats.

## 1.1. Conclusions and Recommendations

The submission reports on the results of two animal studies of carcinogenicity, labeled M24141 and R24142, in mice and rats, respectively. In both studies there were five treatment groups (i.e., two control groups, and three estimated dosages of flutacasone furoate nasal spray), each with 60 animals per treatment group per gender. Treatment groups were labeled as Control 1, Control 2, Low, Medium, and High dose groups respectively. Animals were dosed in a snout only inhalation exposure chamber, with treatment generated as an aerosol dust. The estimated achieved dosages in mice were 0, 0, 2.22, 6.09, and 18.8 μg/kg/day, respectively. The similar estimated achieved dosages in rats were 0, 0, 1.0, 3.19, and 8.61 μg/kg/day.

In both species, for both genders, the estimated survival curves were generally rather intertwined, with no particular treatment group having the uniformly highest survival. In male mice the controls tended to have slightly higher survival than the actual dosing groups. For female mice this slight tendency was reversed with the controls tending to have slightly lower survival than the three dosing groups. Soon after the beginning of the study, in male rats the low dose treatment group (1.00 μg/kg/ day) had the highest survival, while for female rats, at the end of the study the control groups tended to have the highest survival. However these differences were not statistically significant. The significance levels of the tests of homogeneity and trend in survival for the various species by gender combinations are presented in Table 1 below. The only tests of treatment differences that were statistically significant were the logrank test (p=0.0317) and the overall test of trend in survival (p=0.0169) in female rats. Note that the logrank test is sensitive to latter differences in survival than the Wilcoxon.

**Table 1. Significance Levels of Tests of Homogeneity and Trend in Survival**

| | Mice | | | Rats | | |
|---|---|---|---|---|---|---|
| Gender | Log Rank | Wilcoxon | Trend | Log Rank | Wilcoxon | Trend |
| Male | 0.2441 | 0.3434 | 0.6215 | 0.1503 | 0.1503 | 0.3950 |
| Female | 0.9721 | 0.9111 | 0.8057 | 0.0317 | 0.0603 | 0.0169 |

Plots of survival and further details of survival are provided in Sections 3.2.1.2 and 3.2.2.2, and Appendix 1.

One statistical challenge in tests of tumorigenicity is dealing with the issue of multiplicity in testing. Even with absolutely no differences in tumorigenicity between treatment groups, because of the large number of tests, one would expect a considerable number of statistically significant differences. To adjust for the large number of trend tests and pairwise differences from controls, the FDA statisticians usually use the Haseman-Lin-Rahman rules (see Section

1.3.1 below). Using these rules, no pairwise comparison or test of trend in either rats or mice would be considered as statistically significant, although the test of trend in pooled pars distalis and pars intermedia in the pituitary gland of male mice is close to statistical significane (p=0.0281 versus the 0.0250 specified by the Haseman-Lin-Rahman rules). Note that the corresponding asymptotic test would be statistically significant using these rules (p=0.0127), although with only five tumor bearing animals it seems likely that the statistical significance would be inflated (i.e., smaller p-value). Absence of proof is not proof of absence. Nonetheless, with the sole possible exception noted above, these results are consistent with the notion of no particular carcinogenic signal.

The Sponsor also provides pairwise comparisons of each treatment group with control and trend tests deleting the higher dose groups. However, interpreting the results when the tests involving the higher dose group are not statistically significant, but tests involving the lower dose groups are seems to be both biologically and statistically challenging. These cases are discussed in the more detail in Sections 3.2.1 and 3.2.2.

## 1.2. Brief Overview of the Studies

Two inhalation rodent studies were submitted:

**Study M24141: Carcinogenicity Study by Inhalation Administration to CD-1 Mouse for 104 Weeks,**

and,

**Study M24142: Carcinogenicity Study by Inhalation Administration to Han Wistar Rats for 104 Weeks,**

In both studies there were five treatment groups (i.e., two nominally identical controls, and three nominal dosages of fluticasone furoate nasal spray). After a brief acclimatization procedure, animals were dosed in an inhalation chamber described in detail in Section 3.2.1 below. Besides basically identical Control 1 and Control 2 vehicle treatments, estimated doses were 2.22, 6.09, and 18.8 μg/kg/day, respectively, in mice, and 1.0, 3.19, and 8.61 μg/kg/day in rats. The later doses were labeled as Low, Medium, and High dose groups respectively.

## 1.3. Statistical Issues and Findings

### 1.3.1. Statistical Issues

Several issues, typical of such analyses, are considered in the following discussion. These include details of the survival analyses, tests on tumorigenicity, multiplicity of tests on neoplasms, and the validity of the designs.

**1. Survival Analysis:**

Both logrank and Wilcoxon tests were used to test homogeneity of survival among the treatment groups, including the control group. Tests of dose related trend using a Cox proportional odds model were also performed. These involved testing multiple hypotheses, but from the point of view of finding differences among treatment groups would be conservative (i.e., increasing the number of tests increases the chance of rejecting the null, and thus reduces the chance of a Type II error). Appendix 1 reviews the animal survival analyses in some detail.

**2. Tests in Neoplasms:**

The Sponsor indicates that in both studies, for most organs, all animals at risk were exhaustively microscopically examined in all the five treatment groups. In the FDA analysis both the exact permutation tests and symptotic tests were computed but for tumors where total incidence over the four treatment groups was 10 or less only the results of the exact test are presented. For tumors with incidence greater than 10 the results of the asymptotic test are presented. The Peto tumorigenicity analyses were conducted using the FDA WebCarcin program. For each neoplasm, incidental tumors were grouped into weekly intervals 0 -50, 51-78, 79-91, 91-103, and, finally, the terminal sacrifice group. Further details are included in the descriptions of each study in Sections 3.2.1 and 3.2.2, and Appendix 3.

**3. Multiplicity of Tests on Neoplasms:**

Testing the various neoplasms involves a large number of statistical tests, which in turn necessitates an adjustment in experiment-wise Type I error. Current FDA practice is based on the Haseman-Lin-Rahman rules. Namely, based on his extensive experience with such analyses, for pairwise tests comparing control to the high dose group, Haseman (1983) claimed that for a roughly 0.10 (10%) overall false positive error rate, rare tumors should be tested at a 0.05 (5%) level, and common tumors (with a historical control incidence greater than 1%) at a 0.01 level. Based on simulations and their experience, Lin & Rahman (1998) proposed a p-value adjustment for tests of trend. That is, for a roughly 0.10 (10%) overall false positive error rate in tests of trend, rare tumors should be tested at a 0.025 (2.5%) level and common tumors at a 0.005 (0.5%) level. In this analysis we will use the observed incidence in the pooled vehicle groups to decide whether a tumor is rare or common. This approach is intended to balance both Type I error and Type II error (i.e., the error of concluding there is no evidence of a relation to tumorgenicity when there actually is such a relation). Note that the Sponsor also conducted pairwise tests and test of trend deleting the higher dose groups. In these circumstances, strictly speaking, the Haseman-Lin-Rahman rules do not adjust for the multiplicity of comparisons, and the Type I error rate could be expected to increase above the roughly 10% level.

**4. Validity of the Designs:**

Traditionally, the highest dose of a study should be close to the Maximum Tolerated Dose (MTD) to achieve the greatest likelihood of tumorigenicity. Chu, Ceuto, and Ward (1981), citing earlier work by Sontag et al. (1976) recommended that the MTD "is taken as 'the highest dose that causes no more than a 10% weight decrement as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other

than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span' "

Further, Lin and Ali (1994), quoting work by Haseman, have suggested that a survival rate of about 25 animals, out of 50 or more animals, between weeks 80-90 of a two-year study may be considered a sufficient number of survivors as well as one measure of adequate exposure. From the survival plots in Appendix 1, it is evident that in both genders in mice and rats more than 25 animals survived to this date. In fact more than half the animals achieved this survival rate.

Plots of mean weights over time are displayed in Appendix 2. The following table summarizes the animal weights and changes in weight over the course of the experiment. Following the Sponsor, the column labeled differences displays the mean difference from baseline among those animals that survived to the end of the study, and is not the simple difference in mean weights from baseline. The last column shows the ratio of the change from baseline in each treatment group relative to the change from baseline in the control group change. More than a 10% weight deficit in the high dose group relative to controls is typically used to indicate possible problems. For mice males the decrement relative to controls is almost 55%, while for female mice it is 37%. In rats, among males the decrement relative to controls is about 36%, while for female rats it is only 15%.

**Table 2. Summary of Weights and Weight Changes in Dose Groups**

Mice Males

| Dose | Baseline | | Week 79 | | EOS (Week 103) | | Differ- | % Change Rel- |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | N | Mean | N | Mean | Ence | ative to Control |
| Controls 1+2 | 120 | 33.7 | 97 | 41.1 | 56 | 39.9 | 6.3 | - |
| Low | 60 | 33.9 | 44 | 41.0 | 18 | 39.8 | 6.0 | 94.3% |
| Medium | 60 | 33.3 | 43 | 41.0 | 27 | 39.2 | 5.9 | 94.1% |
| High | 60 | 34.4 | 43 | 39.2 | 23 | 36.8 | 2.8 | 44.9% |

Mice Females

| | Baseline | | Week 79 | | EOS (Week 103) | | Differ- | % Change Rel- |
|---|---|---|---|---|---|---|---|---|
| Dose | N | Mean | N | Mean | N | Mean | Ence | ative to Control |
| Controls 1+2 | 120 | 26.1 | 83 | 35.2 | 42 | 34.3 | 8.1 | - |
| Low | 60 | 26.6 | 47 | 34.9 | 19 | 34.0 | 6.9 | 85.2% |
| Medium | 60 | 26.7 | 45 | 34.1 | 22 | 33.2 | 6.3 | 77.9% |
| High | 60 | 26.5 | 43 | 32.6 | 21 | 31.8 | 5.2 | 63.4% |

Rat Males

| Dose | Baseline | | Week 79 | | EOS (Week 104) | | Differ- | % Change Rel- |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | N | Mean | N | Mean | Ence | ative to Control |
| Controls 1+2 | 120 | 275.5 | 109 | 546.4 | 81 | 571.3 | 293.9 | - |
| Low | 60 | 278.3 | 57 | 531.3 | 48 | 548.4 | 269.5 | 91.7% |
| Medium | 60 | 279.2 | 52 | 532.4 | 40 | 541.3 | 262.3 | 89.3% |
| High | 60 | 279.2 | 54 | 491.0 | 38 | 511.2 | 232.8 | 79.2% |

**Table 2. (cont.) Summary of Weights and Weight Changes in Dose Groups**
Rat Females

| Dose | Baseline | | Week 79 | | EOS (Week 104) | | Differ-Ence | % Change Rel-ative to Control |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | N | Mean | N | Mean | | |
| Controls 1+2 | 120 | 180.6 | 109 | 321.0 | 83 | 343.2 | 162.2 | - |
| Low | 60 | 181.2 | 52 | 325.2 | 43 | 353.9 | 171.6 | 105.8% |
| Medium | 60 | 181.7 | 52 | 310.6 | 32 | 324.4 | 147.0 | 90.6% |
| High | 60 | 180.8 | 55 | 299.8 | 30 | 320.9 | 138.3 | 85.3% |

While the weight gain may be suggestive, the relatively low mortality in the high dose group compared to the controls in mice and male rats does not seem to suggest that the MTD was exceeded in either species (please see tables 6,7, 12, and 13 and Appendix 1). For female rats there was a clear increase in mortality in the high dose, but does not seem to be so extreme that the MTD was clearly exceeded.

The above evaluation of the appropriateness of the designs and whether or not the doses were sufficiently close to the MTD is based on some rules derived from data of 200 NCI carcinogen bioassays. Information regarding clinical signs and histopathological data, plus other possible considerations, are well beyond the expertise of this reviewer, but presumably would be used by the toxicologist in the final assessment of the adequacy of these experiments.

### 1.3.2. Statistical Findings

Please see Section 1.1 above.

## 2. INTRODUCTION

### 2.1. Overview

Results from a two year study in CD-1 mice and a similar study in Han Wistar rats were submitted to assess the carcinogenic potential of Flutacasone Furoate Spray ( Sponsor compound GW685698X).

### 2.2. Data Sources

For each study, on October 1, 2006, the Sponsor sent the following self-explanatory SAS transport data sets:

TUMOR.XPT, FOOD.XPT, and WEIGHT.XPT.

# 3. STATISTICAL EVALUATION

## 3.1. Evaluation of Efficacy

**NA**

## 3.2. Evaluation of Safety

Results on both studies are presented below.

### 3.2.1. Study M24141: 104-Week Carcinogenicity Study of GW685698X by Daily Inhalation to CD-1 Mice,

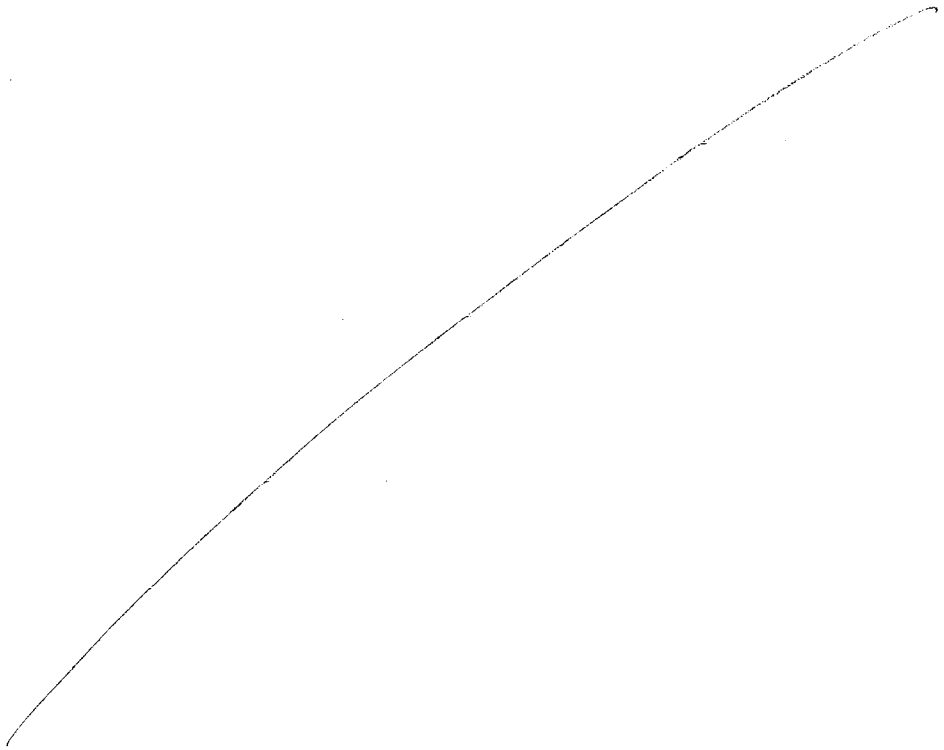
MOUSE STUDY DURATION: approximately 12 adaption days, 104 test weeks.
STUDY STARTING DATE: 10 March 2003 (date of first dose)
STUDY ENDING DATE: 10 March 2005.
MOUSE STRAIN: CD-1 Mice.
ROUTE: Snout only inhalation, once daily (60 minutes/day).

DOSE LEVELS: Two Control Groups Medium: 6.09 µg/kg/day
Low: 2.22 µg/kg/day High: 18.8 µg/kg/day
Number of Animals: 60 male and 60 female mice per treatment group (600 animals)
Satellite animals:
18 male and 18 female mice per dose level group (108 animls)
plus 3 male and 3 female control mice (6 animals)

There were five treatment groups ( i.e., two vehicle control groups, i.e., lactose, and three nominal dosages of flutacasone furoate nasal spray, compound GW685698X in vehicle, namely 2.22, 6.09, and 18.8 µg/kg/day), labeled as Control 1, Control 2, Low, Medium, and High dose groups or as groups 1-5, respectively. The Sponsor reports that on Days –3 to –1, all animals (including spares) were acclimated to the restraint procedure used for inhalation dosing for 20, 40 and 60 minutes respectively. Food and water were available ad libitum. A general check including availability of food and water and environmental conditions was made near the start and end of each working day. Animals were identified by a unique animal number tattooed on the tail.

The Sponsor reports that: "The vertical position of animals on the exposure chamber during dosing was changed weekly to minimise any bias resulting from variations in test material concentration at the 7 exposure levels of the chamber. The first day of dosing was designated Day 1 and days in the pre-treatment period were assigned negative numbers. The data capture system used for recording body weight on the study ( ——— ) designates the bodyweight recorded immediately prior to exposure on Day 1 as Week 0. The final dose was given on the day before scheduled necropsy. Aerosols were generated using a ` ———————

mechanism by suspending material scraped from the surface of a reservoir of compressed test article powder blend in a stream of oil free compressed air." (page 27 of report)



The estimated achieved doses were as follows:

**Table 3. Study M24141: Achieved and Target Dosage**

| Group Number | Target Dose (µg/kg/day) | Estimated Achieved Dose (µg/kg/day) | Target Aerosol Concentration (µg/L) | Achieved Aerosol Concentration (µg/L) |
|---|---|---|---|---|
| 1 (Control) | 0 | 0 | 0 | 0 |
| 2 (Control) | 0 | 0 | 0 | 0 |
| 3 (Low) | 2 | 2.22 | 0.03 | 0.030 |
| 4 (Medium) | 6 | 6.09 | 0.08 | 0.082 |
| 5 (High) | 18 | 18.8 | 0.24 | 0.250 |

### 3.2.1.1 Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analysis on survivability and tumorigencity in mice.

**Sponsor's Survival Analysis Among Mice:**

The Sponsor's tests of mortality are summarized in the following table (Table 4). For each treatment group, the nominal dose (not the estimated actual dose), the number of animals who died of any cause, and the expected number assuming homogeneous losses are presented, along with significance levels of the tests of pairwise comparisons to pooled controls and the tests of overall trend. The test of differences in survival between the low dose (2.22 μg/kg/day) in male mice and pooled controls was close to statistical significance (p=0.055). No other test of trend or pairwise differences was statistically significant.

**Table 4. Log Rank Analysis of Mortality in Mice**

| Males Group | Dose | Initial Group Size | Number of deaths | | Relative death Rate (O/E) | Pairwise Comparison p-value[1] | Trend test p-value |
|---|---|---|---|---|---|---|---|
| | | | Observed | Expected | | | |
| 1+2 | 0 | 120 | 65 | 74.77 | 0.87 | | |
| 3 | 2 | 60 | 42 | 32.67 | 1.29 | 0.055 | |
| 4 | 6 | 60 | 34 | 35.33 | 0.96 | 0.701 | |
| 5 | 18 | 60 | 37 | 35.23 | 1.05 | 0.409 | 0.643 |

| Females Group | Dose | Initial Group Size | Number of deaths | | Relative death Rate (O/E) | Pairwise Comparison p-value[1] | Trend test p-value |
|---|---|---|---|---|---|---|---|
| | | | Observed | Expected | | | |
| 1+2 | 0 | 120 | 80 | 76.98 | 1.04 | | |
| 3 | 2 | 60 | 41 | 41.25 | 0.99 | 0.886 | |
| 4 | 6 | 60 | 39 | 41.13 | 0.95 | 0.711 | |
| 5 | 18 | 60 | 39 | 39.64 | 0.98 | 0.860 | 0.800 |

[1] Two tailed test against pooled controls.

**Sponsor's Tumorigenicity Analysis in Mice:**

The Sponsor conducted Peto type analyses of dose related trend and pairwise differences from the tumor incidence in the control groups. Those comparisons that were statistically significant or were close to statistical significance at the 0.05 level of significance are summarized in Table 5 below. Following the Sponsor, treatment groups are labeled 1 through 5, with 1 and 2 denoting controls, followed by the low, medium, and high doses labeled as 3, 4, and 5 respectively. The tumor incidence is summarized under each treatment group, followed by the p-values of the pairwise test comparing that dose group to the pooled controls. The p-values of the tests of trend are given in the far right column. When only one p-value is presented it is the p-value of the test of trend of the pooled controls through treatment groups 3 to 5 (low to high). When more than one p-value is presented, the first p-value is the result of the test of trend from the pooled controls (groups 1+2) through groups 3 and 4. The lower p-value is the result of the test of trend from the pooled controls (groups 1+2) through groups 3, 4, and 5.

Counting the pairwise comparisons to control and the possible tests of trend involves hundreds of statistical tests. Even if there were no treatment differences, a large number of these tests would be expected to be statistically significant by chance alone. Current FDA practice to correct for the multiplicity of such tests is to use the Haseman-Lin-Rahman rules, reviewed in

section 1.3.1.3 above. However, these rules apply to tests of trend and to pairwise tests between the high dose group and the pooled controls, and not necessarily to the other comparisons. Note that using these rules, none of the tests of overall trend over the five treatment groups or pairwise differences between the high dose group and controls were statistically significant. The test of trend through treatment group 4 (medium dose) and the pairwise test between group 4 and the pooled controls in pooled adenoma and adenocarcinoma in the lungs/bronchi of male mice were small (p=0.002 and p=0.003 respectively), as were the pairwise comparisons between group 4 and the pooled controls in benign cortical adenoma and benign bronchioalvelar adenoma (p=0.029 and p=0.002, respectively). But the rules for adjusting for multiplicity are not completely applicable, and these may be experimental artifacts.

**Table 5. Nominally significant Peto Tests of Tumor Incidence in Mice**

| Males | 1+2 | 3 | 4 | 5 | Overall Trend |
|---|---|---|---|---|---|
| Adrenals:<br>Benign Cortical Adenoma | 0 / 120 | 0 / 60 | 3 / 60<br>0.029 | 0 /60 | 0.468 |
| Adrenals:<br>Benign Subcapsular Cell Adenoma | 7 / 120 | 1 / 60<br>0.770 | 3 / 60<br>0.500 | 6 /60<br>0.196 | 0.063 |
| Lungs/bronchi:<br>Benign Bronchioalveolar Adenoma | 20 / 120 | 11 / 60<br>0.323 | 21 /60<br>0.002 | 15 / 60<br>0.097 | 0.066 |
| Lungs/bronchi: Benign Bronchioalveolar Adenoma + Malignant Adenocarcinoma | 24 / 120 | 12/60<br>0.421 | 23 /60<br>0.003 | 18 / 60<br>0.062 | 0.002<br>0.034 |
| Pituitary – Pars Intermedia:<br>Benign Adenoma | 0 / 119 | 0 / 59 | 0 / 58 | 2 /60<br>0.098 | 0.040 |
| Interstitial (Leydig) Cell:<br>Benign Adenoma + Malignant Carcinoma | 2 / 120 | 2 / 60<br>0.370 | 2 /60<br>0.424 | 4 / 60<br>0.089 | 0.051 |

| Females | 1+2 | 3 | 4 | 5 | Overall Trend |
|---|---|---|---|---|---|
| Harderian Glands:<br>Benign Adenoma | 4 / 120 | 3 / 60<br>0.453 | 6 / 60<br>0.087 | 4 /60<br>0.262 | 0.187 |

### 3.2.1.2 FDA Reviewer's Results

This section will present the Agency findings on survival and tumorigenicity in male and female mice.

**Survival analysis:**

For both mouse genders, the estimated survival curves were generally rather intertwined, with no particular treatment group having the uniformly highest survival. In male mice the controls tended to have slightly higher survival than the actual dosing groups. For female mice this slight tendency was reversed with the controls tending to have sightly lower survival than the three dosing groups. Tests of the hypothesis of homogeneous survival curves were not rejected (Males: Logrank p = 0.2441, p = 0.3434, Females: Logrank p = 0.9721, p = 0.9111).

Kaplan-Meier plots comparing treatment groups in both studies are given in Appendix 1, along with more details of the analysis. The following tables (Table 6 for male mice, Table 7 for

female mice) summarize the mortality results for the dose groups. The data were grouped for the specified time period, and give the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage is the percent survived at the end of the interval, as estimated using a Kaplan-Meier estimate on the ungrouped data. These tables seem to suggest no particular differences in mortality.

**Table 6. Summary of Male Mice Mortality (dose/kg/day)**

| Period (Weeks) | Control 1 | Control 2 | Low 2.22 µg/kg/day | Medium 6.09 µg/kg/day | High 18.8 µg/kg/day |
|---|---|---|---|---|---|
| 1-50 | 3/60 [1]<br>95%[2] | 5/60<br>92% | 6/60<br>90% | 7/60<br>88% | 4/60<br>93% |
| 51-78 | 6/57<br>85% | 8/55<br>78% | 9/54<br>75% | 9/53<br>73% | 13/56<br>72% |
| 79-91 | 13/51<br>65% | 8/47<br>65% | 12/45<br>55% | 7/44<br>62% | 7/43<br>60% |
| 92-103 | 8/38<br>50% | 14/39<br>42% | 15/33<br>30% | 10/37<br>45% | 13/36<br>38% |
| Terminal | 30 | 25 | 18 | 27 | 23 |

[1] number deaths / number at risk in each cell.
[2] In each cell, Kaplan-Meier estimate of cumulative survival at end of interval.

**Table 7. Summary of Female Mice Mortality (dose/kg/day)**

| Period (Weeks) | Control 1 | Control 2 | Low 2.22 µg/kg/day | Medium 6.09 µg/kg/day | High 18.8 µg/kg/day |
|---|---|---|---|---|---|
| 1-50 | 9/60 [1]<br>85%[2] | 6/60 [1]<br>90%[2] | 5/60<br>92% | 5/60<br>92% | 9/60<br>85% |
| 51-78 | 7/51<br>73% | 13/54<br>68% | 8/54<br>78% | 10/55<br>75% | 8/51<br>72% |
| 79-91 | 11/40<br>55% | 9/41<br>53% | 11/45<br>60% | 9/45<br>60% | 9/43<br>57% |
| 92-103 | 12/29<br>35% | 13/32<br>32% | 17/33<br>32% | 15/36<br>35% | 13/34<br>35% |
| Terminal | 21 | 19 | 19 | 21 | 21 |

[1] number deaths / number at risk in each cell.
[2] In each cell, Kaplan-Meier estimate of cumulative survival at end of interval.

**Tumorigenicity analysis:**

The following table (Table 8), displays the comparisons that would be statistically significant at the 0.05 level if one does not adjust for the multiplicity of comparisons. The Haseman-Lin-Rahman rules for adjusting for the large number of comparisons (see Section 1.3.1 above) specify that those tumor-organ combinations with one or fewer tumors in the pooled control group would be classified as rare tumors, the remainder as common. Then, using these rules, no pairwise comparison or test of trend would be considered as statistically significant, although the test of trend in pooled pars distalis and pars intermedia in the pituitary gland of male mice is close to statistical significance (p=0.0281 versus the 0.0250 specified by the Haseman-Lin-Rahman rules). Note that the corresponding asymptotic test would be statistically

significant using these rules (p=0.0127), although with only five tumors it seems apparent that the statistical significance would be inflated (i.e., smaller p-value). Absence of proof is not proof of absence. Nonetheless, with the sole possible exception noted above, these results are consistent with the notion of no particular carcinogenic signal. Tables A.3.1 and A.3.2 in Appendix 3 provide details on the overall tumor incidence in each treatment for each neoplasm organ combination.

**Table 8. Summary of Potentially Statistically Significant Tumoigenicity Results in Mice**

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| Males | | | | | | | |
| LUNGS & BRONCHI | | | | | | | |
| BRONCHIOLOALVEOLAR ADENOMA | 12 | 8 | 11 | 21 | 15 | 0.0637 | 0.0425 |
| Bronch. Adenoma/Carcinoma | 14 | 10 | 12 | 23 | 18 | 0.0343 | 0.0316 |
| PITUITARY | | | | | | | |
| ADENOMA - PARS INTERMEDIA | 0 | 0 | 0 | 0 | 2 | 0.0412 | 0.1095 |
| Adenoma Pars Dist./Inter. | 0 | 1 | 0 | 1 | 3 | 0.0281 | 0.1068 |
| Females | | | | | | | |
| MUSCLE | | | | | | | |
| RHABDOMYOSARCOMA | 0 | 0 | 0 | 0 | 2 | 0.0391 | 0.1176 |
| UTERUS | | | | | | | |
| ENDOMETRIAL POLYP | 3 | 3 | 1 | 4 | 6 | 0.0340 | 0.0945 |
| Uterus/cervix | | | | | | | |
| ENDOMETRIAL POLYP | 3 | 3 | 2 | 4 | 6 | 0.0481 | 0.0919 |

### 3.2.2. Study R24142: 104-Week Carcinogenicity Study of GW685698X by Daily Inhalation to Han Wistar Rats.

RAT STUDY DURATION: 12 adaption days, 104 test weeks.
STUDY STARTING DATE: May 21, 2001.
STUDY ENDING DATE: May 22, 2003.
RAT STRAIN: Han Wistar Rats.
ROUTE: Snout only inhalation, once daily (60 minutes/day).
DOSE LEVELS: Two Control Groups Medium: 3.19 µg/kg/day
Low: 1.00 µg/kg/day High: 8.61 µg/kg/day
Number of Animals: 60 male and 60 female rats per treatment group (600 animals)
Toxicokinetic Satellite animals:
3 male and 3 female control rats (6 animals) and 6 male and 6 female high dose groups (12 animals).

There were five treatment groups ( i.e., two vehicle control groups, i.e. lactose, and three nominal dosages of flutacasone furoate nasal spray, compound GW685698X in vehicle, namely 1.00, 3.19, and 8.61 µg/kg/day), labeled as Control 1, Control 2, Low, Medium, and High dose groups or as groups 1-5, respectively. The dosing, acclimation, and design was the same as that described in study M24141 above. Actual achieved dosing reported by the Sponsor is summarized in the table below:

**Table 9. Achieved and Target Dosage in Rat Study**

| Group Number | Target Dose (µg/kg/day) | Estimated Achieved Dose (µg/kg/day) | Target Aerosol Concentration (µg/L) | Achieved Aerosol Concentration (µg/L) |
|---|---|---|---|---|
| 1 (Control) | 0 | 0 | 0 | 0 |
| 2 (Control) | 0 | 0 | 0 | 0 |
| 3 (Low) | 1 | 1.00 | 0.029 | 0.030 |
| 4 (Medium) | 3 | 3.19 | 0.089 | 0.095 |
| 5 (High) | 9 | 8.61 | 0.251 | 0.252 |

### 3.2.2.1 Sponsor's Results and Conclusions for Rats

This section presents a summary of the Sponsor's analysis of survivability and tumorigencity in rats.

**Sponsor's Survival Analysis of Rats:**

The Sponsor's tests of mortality are taken from the report and summarized in the following table (Table 10). For each treatment group, the estimated actual dose, the number of animals who died of any cause, and the expected number assuming homogeneous losses are presented, along with p-values of the tests of pairwise comparisons to pooled controls and the tests of overall trend. The test of differences in survival between the low dose (1.00 µg/kg/day) in male mice and pooled controls was barely statistically significant (p=0.047). No other test of trend or pairwise differences was statistically significant. In females the tests of trend from the pooled controls through the medium dose group and the through the high dose group were statistically significant (p=0.027 and p=0.012, respectively). In addition, the test of differences in survival between the high dose group and pooled controls was statistically significant (p=0.038). No other differences were statistically significant.

**Table 10. Log Rank Analysis of Mortality in Rats.**

| Males Group | Dose | Initial Group Size | Number of deaths | | Relative death Rate (O/E) | Pairwise Comparison p-value[1] | Trend test p-value |
|---|---|---|---|---|---|---|---|
| | | | Observed | Expected | | | |
| 1 | 0 | 60 | 23 | 18.87 | 1.22 | | |
| 2 | 0 | 60 | 20 | 19.75 | 1.01 | | |
| 3 | 1.00 | 60 | 12 | 21.25 | 0.56 | 0.047 | |
| 4 | 3.19 | 60 | 21 | 19.50 | 1.08 | >0.999 | |
| 5 | 8.61 | 60 | 22 | 18.64 | 1.18 | 0.932 | 0.444 |

[1] Two tailed test against pooled controls.
[2] Two tailed trend test using groups up to the respective row.

**Table 10. (cont.) Log Rank Analysis of Mortality in Rats.**

| Females Group | Dose | Initial Group Size | Number of deaths | | Relative death Rate (O/E) | Pairwise Comparison p-value[1] | Trend test p-value[2] |
|---|---|---|---|---|---|---|---|
| | | | Observed | Expected | | | |
| 1 | 0 | 60 | 17 | 76.98 | 0.71 | | |
| 2 | 0 | 60 | 21 | 18.87 | 0.93 | | |
| 3 | 1.00 | 60 | 17 | 41.25 | 0.72 | 0.806 | 0.703 |
| 4 | 3.19 | 60 | 28 | 41.13 | 1.32 | 0.072 | 0.027 |
| 5 | 8.61 | 60 | 30 | 39.64 | 1.38 | 0.038 | 0.012 |

[1] Two tailed test against pooled controls.
[2] Two tailed trend test using groups up to the respective row.

**Sponsor's Tumorigenicity Analysis in Rats:**

A table summarizing the potentially statistically significant trends and pairwise comparisons conducted by the Sponsor are summarized in Table 11 below. Following the Sponsor's notation, treatment groups are labeled 1 through 5, with 1 and 2 denoting controls, followed by the low, medium, and high doses labeled as 3, 4, and 5 respectively. The tumor incidence is summarized under each treatment group, followed by the significance level of the pairwise test comparing that dose group to the pooled controls. The significance levels of the tests of trend are given in the far right column. When only one p-value is presented, it is the significance level of the test of trend of the pooled controls through treatment groups 3 to 5 (low to high). When more than one p-value is presented, the first p-value is the result of the test of trend from the pooled controls (groups 1+2) through groups 3 and 4. The lower p-value is the result of the test of trend from the pooled controls (groups 1+2) through groups 3, 4, and 5.

As in the mouse study, counting the pairwise comparisons to control and the possible tests of trend involves hundreds of statistical tests. Even if there were no treatment differences, a large number of these tests would be expected to be statistically by chance alone. Current FDA practice to correct for the multiplicity of such tests is to use the Haseman-Lin-Rahman rules, reviewed in section 1.3.1.3 above. Using these rules, none of the tests of trend over the five treatment groups or pairwise differences between the high dose group and controls, or, for that matter any other dose group and controls were statistically significant. Note however that the pairwise test comparing the high dose to the controls in benign haemangioma of the mesenteric lymph in male rats comes close to statistical significance (p=0.014).

**Table 11. Nominally significant Peto Tests of Tumor Incidence in Rats**

| Males | 1+2 | 3 | 4 | 5 | Overall Trend |
|---|---|---|---|---|---|
| Liver: Malignant Hepatocellular Carcinoma | 0 / 120 | 0 / 60 | 0 / 60 | 2 / 60 0.107 | 0.035 |
| Mesenteric Lymph Node: Benign Haemangioma | 21 / 120 | 8 / 60 0.658 | 9 / 60 0.828 | 2 / 60 0.014 | 0.712 0.015 |
| Pancreas: Benign Islet Cell Adenoma | 3 / 120 | 3 / 60 0.346 | 6 / 60 0.033 | 2 / 60 0.500 | 0.427 |
| Pancreas: Islet Cell Benign Adenoma & Malignant Carcinoma | 3 / 120 | 3 / 60 0.316 | 6 / 60 0.034 | 3 / 60 0.331 | 0.248 |

| Females | 1+2 | 3 | 4 | 5 | Overall Trend |
|---|---|---|---|---|---|
| Adrenals: Benign Cortical Adenoma | 2 / 120 | 0 / 60 >0.999 | 0 / 60 >0.999 | 4 / 60 0.094 | 0.018 |
| Thymoma: Benign Thymoma | 11 / 120 | 5 / 60 >0.999 | 0 /60 0.048 | 2 / 60 0.213 | 0.098 |
| Thyroids: Benign & Malignant C-cell Adenoma Carcinoma | 13 / 120 | 9 / 60 0.262 | 3 /60 0.811 | 11 / 60 0.107 | 0.070 |
| Uterus: Malignant Endometrial Adenocarcinoma | 2 / 120 | 4 / 60 0.078 | 2 / 60 0.406 | 3 / 60 0.204 | 0.200 |
| Uterus: Malignant Schwannoma | 0 / 120 | 0 / 60 | 2 / 60 0.086 | 0 / 60 | 0.3320 |
| Uterus: Malignant Endometrial Adenocarcinoma | 2 / 120 | 4 / 60 0.078 | 2 / 60 0.406 | 3 / 60 0.204 | 0.200 |

### 3.2.2.2 FDA Reviewer's Results

This section summarizes the Agency results on survival and tumorigenicity in male and female rats.

**Survival analysis:**

As with mice, the estimated survival curves for male rats were generally rather intertwined, with no particular treatment group having the uniformly highest survival. Starting early in the study, male rats in the low dose treatment group (1.00 µg/kg/ day) tended to have the highest survival, while for female rats, at the end of the study the control groups tended to have the highest survival. The log rank tests of homogeneity in survival was statistically significant (p=0.0317) in female rats, as was the overall test of trend in survival in (p=0.0169). In male rats differences in survival were not statistically significant.

These results are summarized in the following tables (Tables 12 and 13). The data are grouped for the specified time period, and give the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage is the percent surviving at the end of the interval, as estimated using a Kaplan-Meier estimate on the ungrouped data.

**Table 12. Summary of Male Rat Mortality (dose/kg/day)**

| Period (Weeks) | Control 1 | Control 2 | Low 1.00 µg/kg/day | Medium 3.19 µg/kg/day | High 8.61 µg/kg/day |
|---|---|---|---|---|---|
| 1-50 | 0/60 [1]<br>100%[2] | 2/60 [1]<br>97%[2] | 2/60<br>97% | 1/60<br>98% | 1/60<br>98% |
| 51-78 | 7/60<br>88% | 2/58<br>93% | 1/58<br>95% | 7/59<br>87% | 5/59<br>90% |
| 79-91 | 7/53<br>77% | 7/56<br>82% | 2/57<br>92% | 3/52<br>82% | 7/54<br>78% |
| 92-104 | 12/46<br>57% | 12/49<br>62% | 11/55<br>73% | 13/49<br>60% | 12/47<br>58% |
| Terminal | 34 | 37 | 44 | 36 | 35 |

[1] number deaths / number at risk in each cell.
[2] In each cell, Kaplan-Meier estimate of cumulative survival at end of interval.

**Table 13. Summary of Female Rat Mortality (dose/kg/day)**

| Period (Weeks) | Control 1 | Control 2 | Low 1.00 µg/kg/day | Medium 3.19 µg/kg/day | High 8.61 µg/kg/day |
|---|---|---|---|---|---|
| 1-50 | 0/60 [1]<br>100%[2] | 0/60 [1]<br>100%[2] | 1/60<br>98% | 1/60<br>98% | 0/60<br>100% |
| 51-78 | 4/60<br>93% | 6/60<br>90% | 7/59<br>87% | 6/59<br>88% | 5/60<br>92% |
| 79-91 | 6/56<br>83% | 7/54<br>78% | 1/52<br>85% | 10/53<br>72% | 8/55<br>78% |
| 92-104 | 10/50<br>67% | 11/47<br>60% | 12/51<br>65% | 14/43<br>26% | 20/47<br>45% |
| Terminal | 40 | 36 | 39 | 29 | 27 |

[1] number deaths / number at risk in each cell.
[2] In each cell, Kaplan-Meier estimate of cumulative survival at end of interval.

**Tumorigenicity analysis:**

Prior to adjusting for multiplicity, only three tests of tumor incidence were found to be statistically significant. These are presented in the following table (Table 14). For the Haseman-Lin-Rahman rules for adjusting for the large number of comparisons (see Section 1.3.1 above), those tumor-organ combinations with one or fewer tumors in the control group would be classified as rare tumors, the remainder as common. Then, using these rules, no pairwise comparison or test of trend would be considered as statistically significant. Again, absence of proof is not proof of absence. Nonetheless these results are consistent with the notion of no particular carcinogenic signal. Tables A.3.3 and A.3.4 in Appendix 3 provide details of the overall tumor incidence in each treatment for each neoplasm organ combination.

**Table 14. Summary of Potentially Statistically Significant Tumoigenicity Results in Rats**

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| Male Rats | | | | | | | |
| LIVER | | | | | | | |
| HEPATOCELLULAR CARCINOMA | 0 | 0 | 0 | 0 | 2 | 0.0346 | 0.1072 |
| Hep. Adenoma/Carcinoma | 1 | 4 | 2 | 4 | 6 | 0.0381 | 0.0644 |
| Female Rats | | | | | | | |
| ADRENALS | | | | | | | |
| CORTICAL ADENOMA | 2 | 0 | 0 | 0 | 4 | 0.0199 | 0.1504 |

# 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

**NA**

# 5 SUMMARY AND CONCLUSIONS

## 5.1. Statistical Issues and Collective Evidence

Please see Section 1.3 above.

## 5.2. Conclusions and Recommendations

Please see Section 1.1 above.

# APPENDICES:

## Appendix 1. Survival Analysis

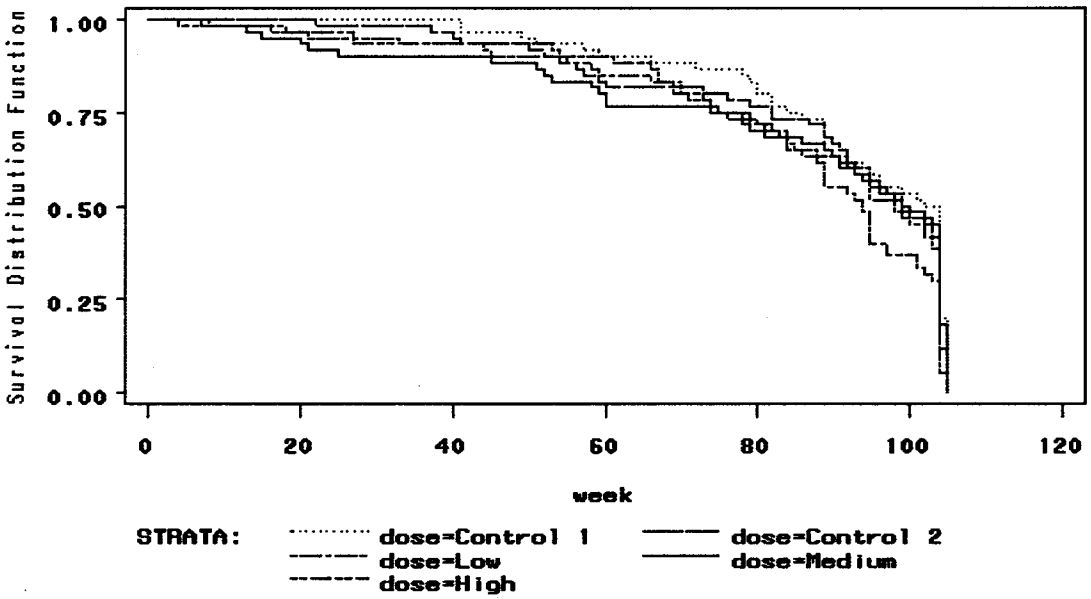
For males of both species and for mice females the dose groups were generally intertwined, with survival in no dose group uniformly better or worse than any other dose group. In male mice there was a slight tendency for the control groups to have the lowest mortality, while in female mice and male rats there was a slight tendency for the control groups to have higher mortality. However, as shown in the following table of significance levels, these differences were not statistically significant. In female rats there was a tendency toward increasing mortality with dose, confirmed by a statistically significant test of trend.

**Table A.1.1 . Significance Levels of Tests of Homogeneity and Trend in Survival**

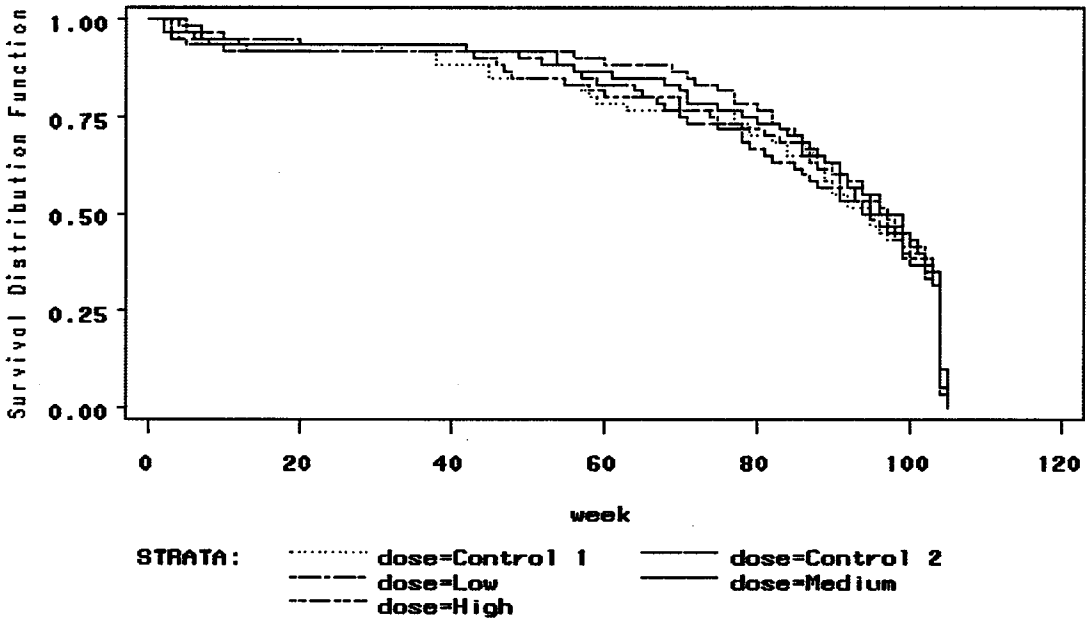
| | Mice | | | Rats | | |
|---|---|---|---|---|---|---|
| Gender | Log Rank | Wilcoxon | Trend | Log Rank | Wilcoxon | Trend |
| Male | 0.2441 | 0.3434 | 0.6215 | 0.1503 | 0.1503 | 0.3950 |
| Female | 0.9721 | 0.9111 | 0.8057 | 0.0317 | 0.0603 | 0.0169 |

The figures below display the Kaplan-Meier estimated survival curves for the four different species by gender combinations. These curves include the time of censoring, including sacrifice or acidental death, as an event.

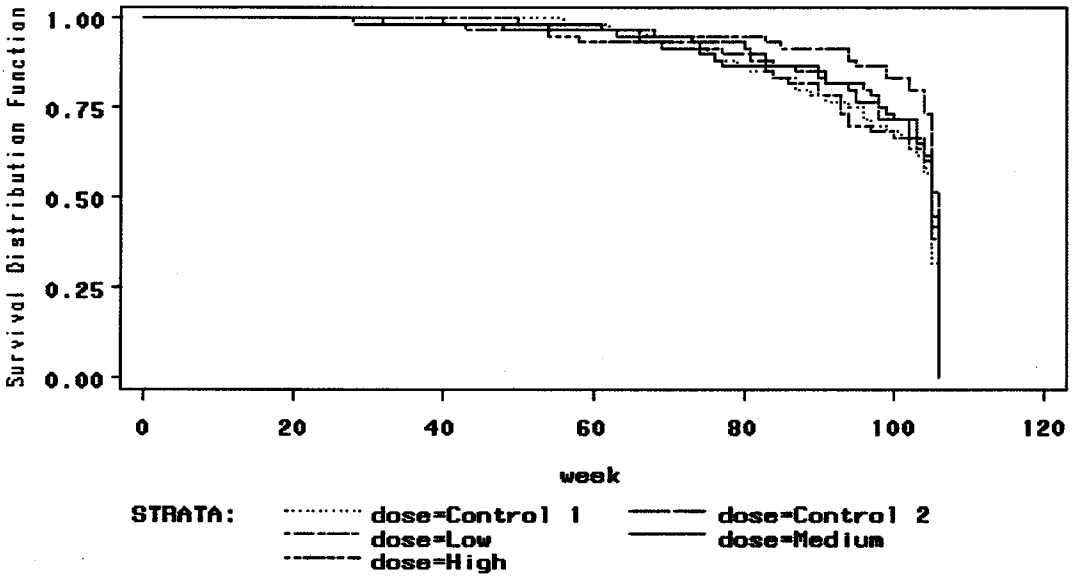
**Figure A.1.1 Male Mice**



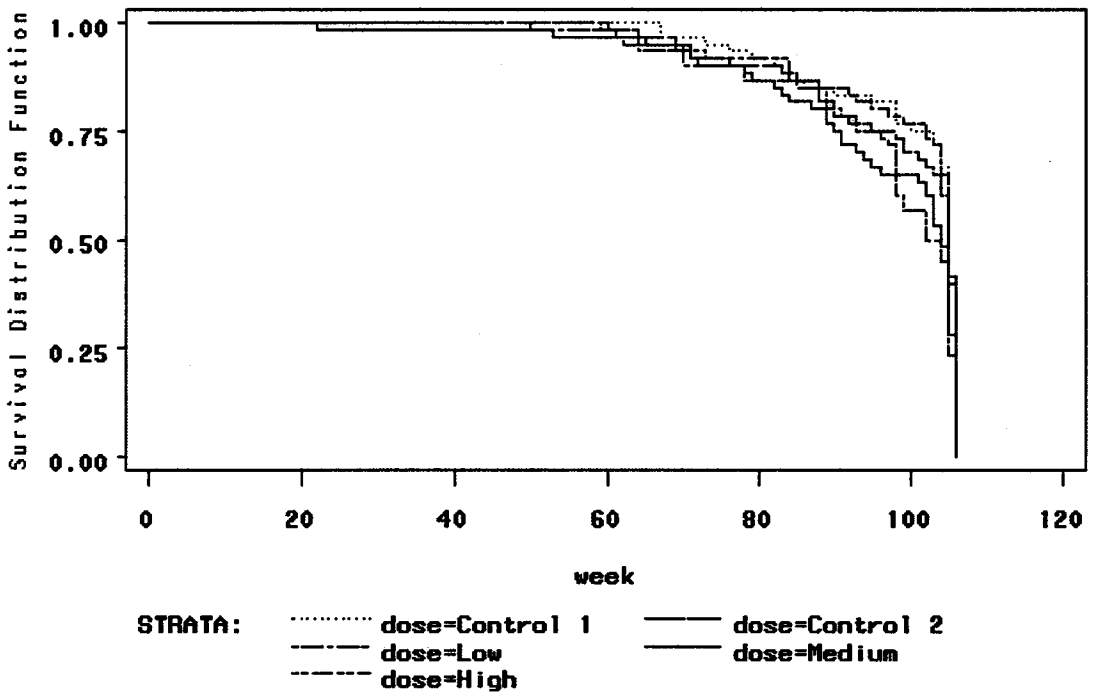
# Figure A.12 Female Mice




# Figure A.13 Male Rats



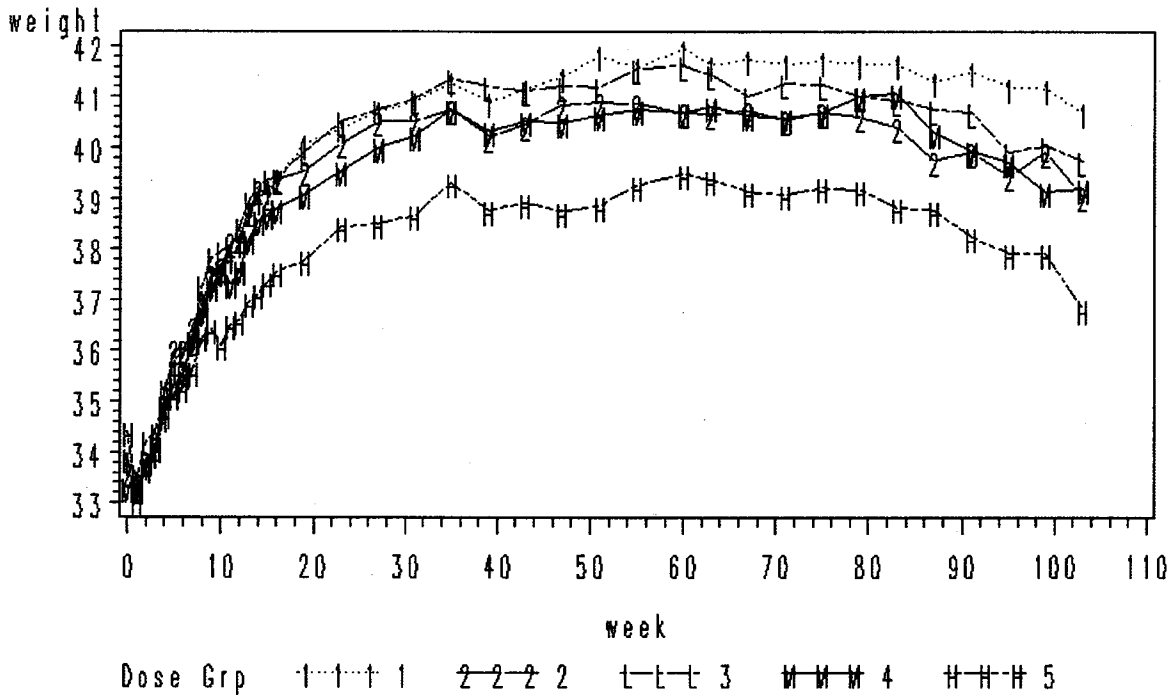
# Figure A.14 Female Rats



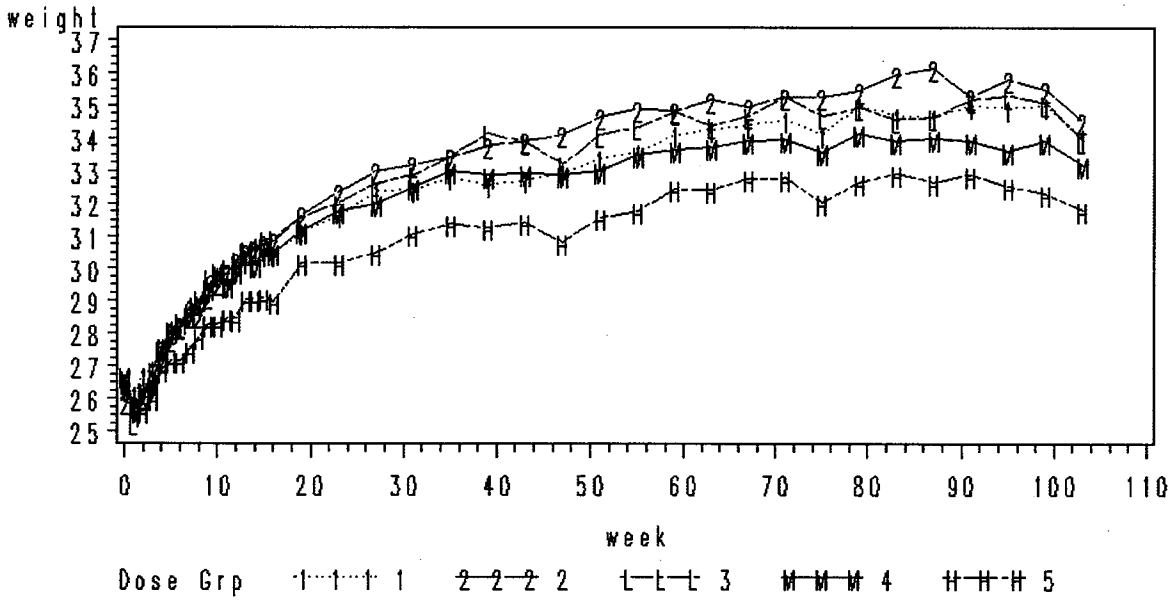
## Appendix 2. Weight Gains

The following plots display the mean animal weights over the course of the studies. The plots labeled "1" and "2" correspond to the controls, while the "L", "M", and "H" correspond to the low, medium, and high dose groups respectively. Note that for each gender and species the high dose group soon has consistently lower weight than the other dose groups. In male mice the profiles of the mean weight in other dose groups are very closely intertwined. In female mice and both rat genders there is a slight general trend towards decreasing weight as dose increases, although the groups are not as clearly separated as with the high dose group.

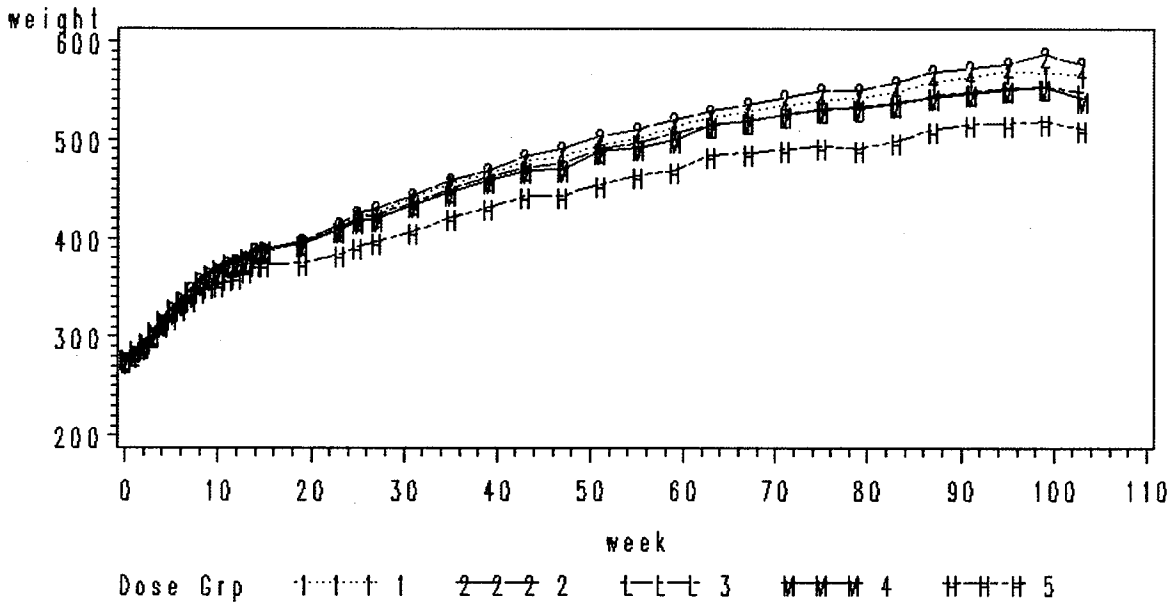
### Figure A.2.1 Mean Weight By Week
### Male Mice



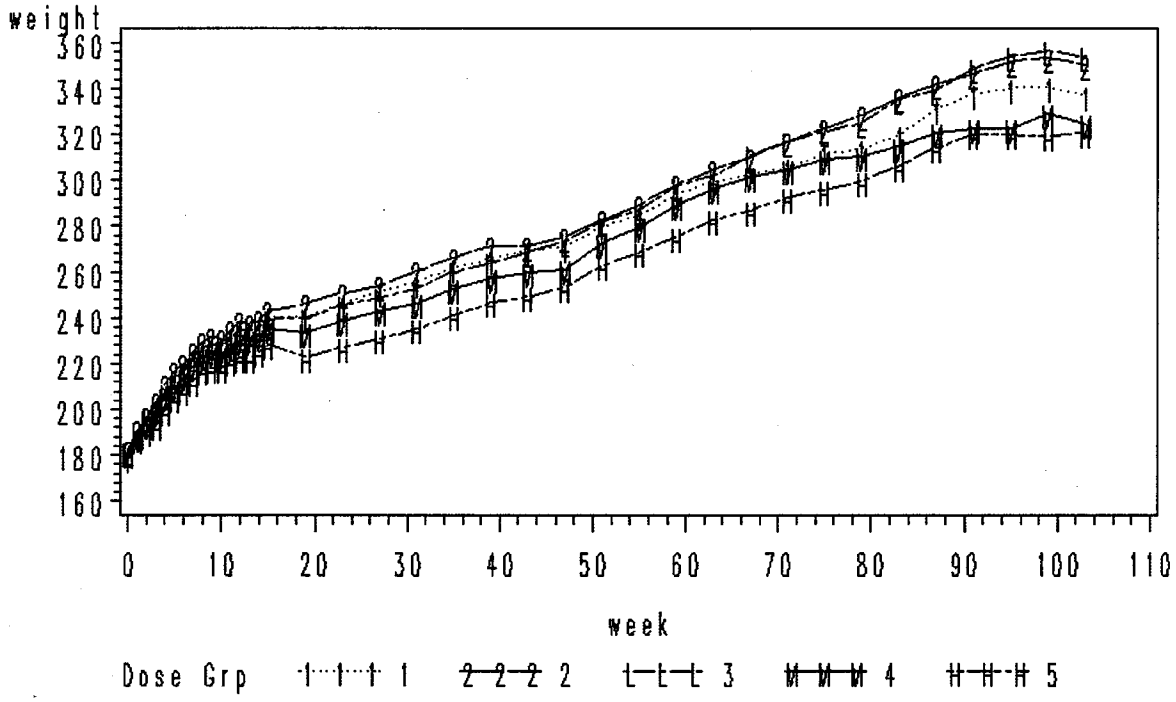
# Figure A.2.2 Mean Weight By Week
# Female Mice




# Figure A.2.3. Mean Weight By Week
# Male Rats



# Figure A.2.4. Mean Weight By Week
# Female Rats



## Appendix 3. FDA Tumorigenicity Analysis

Tables A.3.1 through A.3.2 below display the number of neoplasms in each organ and tumor combination in mice taken from the datasets provided by the Sponsor. Tables A.3.3 and A.3.4 below display similar results for rats. For each dose group, the numbers in the table are the number of animals where histopathological analysis detected a tumor. For both species and each gender there were 60 animals, most of whom were analyzed histopathologically. The significance levels of both the tests of trend over the pooled controls and the three treatment groups and the tests comparing the high dose group to the pooled controls are presented. For more than 10 animals with tumors, the results are from asymptotic tests. For 10 or fewer animals the results are from exact tests, with fixed marginal totals.

The Haseman-Lin-Rahman rules summarized below are designed to adjust for the multiplicity of tests over the organ by tumor combinations and determine if the observed p-value is statistically significant. That is, to control the overall Type I error rate to roughly 10% for each type of comparison, one compares the unadjusted significance level to the appropriate bound below:

| Haseman – Lin - Rahman Bounds: Comparison | Rare Tumor (Incidence ≤ 1%) | Common Tumor (Incidence > 1%) |
|---|---|---|
| Trend (over 3 or more groups) | 0.025 | 0.005 |
| Pairwise | 0.05 | 0.01 |

So, for example, for a rare tumor (with incidence in the pooled control groups ≤ 1%, i.e. 0 or 1 tumor out of 120 controls), a trend would be considered statistically significant if the computed significance level was at or less than 0.025, while a comparison between the high dose group and the pooled controls (i.e., a pairwise comparison) would be statistically significant if the computed significance level was no more than 0.05. Tumors with an incidence greater than 1 in the pooled controls are considered as common tumors.

Using the Haseman-Lin-Rahman rules, no pairwise comparison or test of trend in either rats or mice would be considered as statistically significant, although the test of trend in pooled pars distalis and pars intermedia in the pituitary gland of male mice is close to statistical significane (p=0.0281 versus the 0.0250 specified by the Haseman-Lin-Rahman rules). Note that the corresponding asymptotic test would be statistically significant using these rules (p=0.0127), although with only five tumor bearing animals it was felt the statistical significance would be inflated (i.e., smaller p-value). Absence of proof is not proof of absence. Nonetheless, with the sole possible exception noted above, these results are consistent with the notion of no particular carcinogenic signal.

## Table A.3.1. Tumorgenicity in Male Mice

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| ADRENALS | | | | | | | |
| CORTICAL ADENOMA | 0 | 0 | 0 | 3 | 0 | 0.6314 | |
| CORTICAL CARCINOMA | 1 | 0 | 1 | 0 | 0 | 0.8458 | 1.0000 |
| Cort. Adenoma/Carcinoma | 1 | 0 | 1 | 3 | 0 | 0.6815 | 1.0000 |
| PHAEOCHROMOCYTOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| SUBCAPSULAR CELL ADENOMA | 2 | 5 | 1 | 3 | 6 | 0.0535 | 0.1195 |
| BONE | | | | | | | |
| OSTEOFIBROMA | 0 | 0 | 1 | 0 | 0 | 0.5929 | |
| OSTEOMA | 0 | 0 | 1 | 0 | 0 | 0.5528 | |
| OSTEOSARCOMA | 0 | 0 | 0 | 1 | 0 | 0.3948 | |
| CAECUM | | | | | | | |
| ADENOCARCINOMA | 0 | 1 | 1 | 0 | 1 | 0.3923 | 0.5767 |
| COLON | | | | | | | |
| ADENOCARCINOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| Caecum/Colon | | | | | | | |
| ADENOCARCINOMA | 0 | 2 | 1 | 0 | 1 | 0.5325 | 0.7178 |
| EPIDIDYMIDES | | | | | | | |
| LEYDIG CELL CARCINOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| GALL BLADDER | | | | | | | |
| PAPILLOMA | 0 | 0 | 1 | 0 | 0 | 0.5652 | |
| H'POIETIC TUMOUR | | | | | | | |
| LYMPHOCYTIC/LYMPHOBLASTIC | 6 | 2 | 2 | 3 | 5 | 0.2468 | 0.3105 |
| MALIGNANT LYMPHOMA | 0 | 0 | 0 | 1 | 1 | 0.1196 | 0.3291 |
| MALIGNANT MAST CELL TUMOU | 0 | 0 | 0 | 1 | 0 | 0.4065 | |
| MYELOID LEUKAEMIA | 1 | 0 | 2 | 0 | 0 | 0.8241 | 1.0000 |
| PLEOMORPHIC LYMPHOMA | 3 | 3 | 5 | 1 | 2 | 0.7813 | 0.7894 |
| HARDERIAN GLANDS | | | | | | | |
| ADENOMA | 6 | 3 | 2 | 5 | 6 | 0.2003 | 0.2914 |
| KIDNEYS | | | | | | | |
| TUBULAR ADENOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| TUBULAR CARCINOMA | 0 | 0 | 1 | 0 | 1 | 0.1977 | 0.2949 |
| Tub. Adenoma/Carcinoma | 0 | 1 | 1 | 0 | 1 | 0.3785 | 0.5055 |
| LIVER | | | | | | | |
| HAEMANGIOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| HEPATOCELLULAR ADENOMA | 5 | 4 | 5 | 3 | 5 | 0.3935 | 0.3692 |
| HEPATOCELLULAR CARCINOMA | 0 | 2 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| Hep. Adenoma/Carcinoma | 5 | 6 | 5 | 3 | 5 | 0.5185 | 0.5158 |
| LUNGS & BRONCHI | | | | | | | |
| BRONCHIOLOALVEOLAR ADENOC | 2 | 2 | 2 | 3 | 3 | 0.2591 | 0.4027 |
| BRONCHIOLOALVEOLAR ADENOM | 12 | 8 | 11 | 21 | 15 | 0.0637 | 0.0425 |
| Bronch. Adenoma/Carcinoma | 14 | 10 | 12 | 23 | 18 | 0.0343 | 0.0316 |
| PITUITARY | | | | | | | |
| ADENOMA - PARS DISTALIS | 0 | 1 | 0 | 1 | 1 | 0.2719 | 0.5568 |
| ADENOMA - PARS INTERMEDIA | 0 | 0 | 0 | 0 | 2 | 0.0412 | 0.1095 |
| Adenoma Pars Dist./Inter. | 0 | 1 | 0 | 1 | 3 | 0.0281 | 0.1068 |
| SEMINAL VESICLES | | | | | | | |
| ADENOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |

## Table A.3.1. (cont.) Tumorgenicity in Male Mice

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| SKIN | | | | | | | |
| BASAL CELL CARCINOMA | 0 | 0 | 0 | 0 | 1 | 0.1916 | 0.3130 |
| FIBROSARCOMA | 0 | 1 | 2 | 0 | 1 | 0.4318 | 0.5205 |
| HAEMANGIOSARCOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| SARCOMA NOS | 1 | 1 | 1 | 0 | 0 | 0.9256 | 1.0000 |
| SEBACEOUS CELL ADENOMA | 0 | 1 | 0 | 0 | 1 | 0.3496 | 0.5219 |
| SQUAMOUS CELL PAPILLOMA | 0 | 2 | 0 | 1 | 2 | 0.1542 | 0.3342 |
| SPLEEN | | | | | | | |
| HAEMANGIOMA | 1 | 0 | 0 | 0 | 1 | 0.3631 | 0.5568 |
| STOMACH | | | | | | | |
| ADENOMA | 0 | 0 | 2 | 1 | 0 | 0.5497 | |
| SARCOMA N.O.S | 0 | 0 | 0 | 1 | 0 | 0.3964 | |
| SQUAMOUS CELL PAPILLOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| Sarcoma/Adenoma | 0 | 0 | 2 | 2 | 0 | 0.5935 | |
| TAIL | | | | | | | |
| TRICHOEPITHELIOMA | 0 | 0 | 1 | 0 | 0 | 0.6333 | |
| TESTES | | | | | | | |
| ADENOMA - RETE TESTIS | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| INTERSTITIAL (LEYDIG) CEL | 0 | 2 | 2 | 2 | 3 | 0.1405 | 0.2149 |
| INTERSTITIAL (LEYDIG) CEL | 0 | 0 | 0 | 0 | 1 | 0.1870 | 0.2949 |
| Inter. Adenoma/Carcinoma | 0 | 2 | 2 | 2 | 4 | 0.0565 | 0.0934 |
| THYROIDS | | | | | | | |
| FOLLICULAR CELL ADENOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| URINARY BLADDER | | | | | | | |
| TRANSITIONAL CELL CARCINO | 0 | 0 | 1 | 0 | 0 | 0.5528 | |

## Table A.3.2. Tumorgenicity in Female Mice

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| ADRENALS | | | | | | | |
| PHAEOCHROMOCYTOMA | 0 | 0 | 1 | 0 | 0 | 0.6040 | |
| SUBCAPSULAR CELL ADENOMA | 1 | 0 | 1 | 1 | 2 | 0.1230 | 0.2198 |
| BONE | | | | | | | |
| CHONDROSARCOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| CAECUM | | | | | | | |
| ADENOCARCINOMA | 1 | 0 | 1 | 1 | 0 | 0.6847 | 1.0000 |
| COLON | | | | | | | |
| ADENOCARCINOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| ADENOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| Caecum/Colon | | | | | | | |
| Adenoma/Adenocarcinoma | 3 | 0 | 1 | 1 | 0 | 0.9008 | 1.0000 |
| H'POIETIC TUMOUR | | | | | | | |
| HISTIOCYTIC SARCOMA | 5 | 4 | 3 | 6 | 1 | 0.9220 | 0.9850 |
| LYMPHOCYTIC/LYMPHOBLASTIC | 7 | 6 | 5 | 4 | 2 | 0.9538 | 0.9533 |
| MALIGNANT LYMPHOMA | 1 | 0 | 0 | 1 | 0 | 0.6415 | 1.0000 |
| MYELOID LEUKAEMIA | 1 | 1 | 1 | 1 | 0 | 0.8221 | 1.0000 |
| PLASMA CELL LYMPHOMA | 0 | 0 | 1 | 0 | 0 | 0.6040 | |
| PLEOMORPHIC LYMPHOMA | 2 | 8 | 3 | 7 | 0 | 0.9757 | 1.0000 |
| HARDERIAN GLANDS | | | | | | | |
| ADENOCARCINOMA | 3 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| ADENOMA | 1 | 3 | 3 | 6 | 4 | 0.1666 | 0.2334 |

**Table A.3.2. (cont.) Tumorgenicity in Female Mice**

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| LIVER | | | | | | | |
| HAEMANGIOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| HAEMANGIOSARCOMA | 0 | 1 | 0 | 1 | 1 | 0.2616 | 0.5686 |
| HEPATOCELLULAR ADENOMA | 0 | 0 | 0 | 1 | 0 | 0.4000 | |
| HEPATOCELLULAR CARCINOMA | 0 | 0 | 0 | 0 | 1 | 0.2130 | 0.3485 |
| LUNGS & BRONCHI | | | | | | | |
| BRONCHIOLOALVEOLAR ADENOC | 2 | 2 | 2 | 3 | 2 | 0.5160 | 0.6750 |
| BRONCHIOLOALVEOLAR ADENOM | 11 | 12 | 13 | 7 | 13 | 0.3999 | 0.3630 |
| Bronch. Adenoma/Carcinoma | 13 | 14 | 15 | 10 | 15 | 0.4183 | 0.3968 |
| Liver/Subcut./Ovaries | | | | | | | |
| Hep. Ad./Carc./Hemang. | 0 | 1 | 0 | 3 | 1 | 0.2665 | 0.5507 |
| MAMMARY PROTOCOL | | | | | | | |
| ADENOACANTHOMA | 2 | 1 | 1 | 0 | 1 | 0.6609 | 0.8232 |
| Adenocanthoma/-carc | 4 | 3 | 5 | 1 | 2 | 0.8399 | 0.8693 |
| MAMMARY ADENOCARCINOMA | 3 | 2 | 4 | 1 | 1 | 0.8693 | 0.9163 |
| MUSCLE | | | | | | | |
| RHABDOMYOSARCOMA | 0 | 0 | 0 | 0 | 2 | 0.0391 | 0.1176 |
| OVARIES | | | | | | | |
| GRANULAR CELL TUMOUR | 0 | 0 | 0 | 1 | 0 | 0.4158 | |
| GRANULOSA CELL TUMOUR | 1 | 0 | 1 | 0 | 0 | 0.8455 | 1.0000 |
| HAEMANGIOMA | 0 | 1 | 0 | 2 | 0 | 0.5482 | 1.0000 |
| LEIOMYOSARCOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| LUTEOMA | 0 | 0 | 0 | 1 | 0 | 0.4158 | |
| Leiomysarcoma/Luteoma | 0 | 1 | 0 | 1 | 0 | 0.6444 | 1.0000 |
| SERTOLI CELL ADENOMA | 1 | 1 | 0 | 1 | 1 | 0.4313 | 0.7202 |
| TUBULAR ADENOMA | 0 | 0 | 0 | 1 | 0 | 0.4000 | |
| YOLK SAC CELL TUMOUR | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| PITUITARY | | | | | | | |
| ADENOMA - PARS DISTALIS | 1 | 2 | 2 | 2 | 0 | 0.8879 | 1.0000 |
| ADENOMA - PARS INTERMEDIA | 0 | 1 | 0 | 1 | 1 | 0.2719 | 0.5733 |
| Adenoma Pars Dist./Inter. | 1 | 3 | 2 | 3 | 1 | 0.7249 | 0.8891 |
| SALIVARY GLAND | | | | | | | |
| MYOEPITHELIAL CELL TUMOUR | 0 | 0 | 1 | 0 | 0 | 0.6159 | |
| SKIN | | | | | | | |
| BASOSQUAMOUS CELL CARCINO | 0 | 0 | 0 | 0 | 1 | 0.2097 | 0.3545 |
| SARCOMA NOS | 0 | 1 | 0 | 0 | 1 | 0.3534 | 0.5478 |
| SQUAMOUS CELL PAPILLOMA | 0 | 1 | 3 | 0 | 1 | 0.4968 | 0.5478 |
| SPLEEN | | | | | | | |
| HAEMANGIOSARCOMA | 2 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| STOMACH | | | | | | | |
| HAEMANGIOSARCOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| SQUAMOUS CELL PAPILLOMA | 3 | 0 | 1 | 0 | 1 | 0.6665 | 0.8145 |
| SUBCUTIS | | | | | | | |
| HAEMANGIOSARCOMA | 0 | 0 | 0 | 1 | 0 | 0.3983 | |
| SARCOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| Systemic | | | | | | | |
| Hemangioma/Hemangiosarcom | 4 | 5 | 1 | 2 | 1 | 0.9368 | 0.9848 |
| Stomach/Tongue | | | | | | | |
| SQUAMOUS CELL PAPILLOMA | 3 | 1 | 1 | 0 | 1 | 0.7567 | 0.8829 |
| TONGUE | | | | | | | |
| SQUAMOUS CELL PAPILLOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |

**Table A.3.2. (cont.) Tumorgenicity in Female Mice**

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| UTERINE CERVIX | | | | | | | |
| ADENOMA | 0 | 0 | 1 | 0 | 0 | 0.6040 | |
| ENDOMETRIAL POLYP | 0 | 0 | 1 | 0 | 0 | 0.6040 | |
| LEIOMYOMA | 1 | 1 | 1 | 0 | 1 | 0.5396 | 0.7060 |
| LEIOMYOSARCOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| UTERUS | | | | | | | |
| ENDOMETRIAL POLYP | 3 | 3 | 1 | 4 | 6 | 0.0340 | 0.0945 |
| HAEMANGIOMA | 2 | 1 | 1 | 1 | 0 | 0.9021 | 1.0000 |
| HAEMANGIOSARCOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| LEIOMYOMA | 2 | 2 | 2 | 1 | 1 | 0.7515 | 0.8677 |
| LEIOMYOSARCOMA | 1 | 0 | 1 | 0 | 0 | 0.8597 | 1.0000 |
| UTERINE CARCINOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| Uterus/cervix | | | | | | | |
| ENDOMETRIAL POLYP | 3 | 3 | 2 | 4 | 6 | 0.0481 | 0.0919 |

**Table A.3.3. Tumorgenicity in Male Rats**

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| ADIPOSE TISSUE | | | | | | | |
| HAEMANGIOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| LIPOMA | 1 | 0 | 0 | 1 | 0 | 0.6182 | 1.0000 |
| MALIGNANT SCHWANNOMA | 1 | 0 | 0 | 0 | 1 | 0.3416 | 0.5536 |
| ADRENALS | | | | | | | |
| CORTICAL ADENOMA | 3 | 4 | 4 | 2 | 1 | 0.9222 | 0.9644 |
| MALIGNANT PHAEOCHROMOCYTO | 0 | 0 | 1 | 0 | 1 | 0.1975 | 0.3304 |
| PHAEOCHROMOCYTOMA | 0 | 4 | 3 | 5 | 2 | 0.4688 | 0.6489 |
| Phaeochromocytoma/Malig. | 0 | 4 | 4 | 5 | 3 | 0.3252 | 0.4225 |
| BONE | | | | | | | |
| CHONDROMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| OSTEOMA | 0 | 0 | 0 | 0 | 1 | 0.1881 | 0.3304 |
| OSTEOSARCOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| BRAIN | | | | | | | |
| ASTROCYTOMA | 1 | 1 | 0 | 1 | 0 | 0.7664 | 1.0000 |
| GRANULAR CELL TUMOUR | 0 | 1 | 0 | 1 | 0 | 0.6182 | 1.0000 |
| HAEMANGIOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| MENINGEAL SARCOMA | 0 | 0 | 1 | 0 | 0 | 0.6188 | |
| MIXED GLIOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| OLIGODENDROGLIOMA | 0 | 0 | 0 | 1 | 0 | 0.3812 | |
| PINEAL GLAND TUMOUR | 0 | 0 | 1 | 0 | 0 | 0.6188 | |
| CAECUM | | | | | | | |
| LEIOMYOSARCOMA | 0 | 0 | 1 | 0 | 0 | 0.6157 | |
| COAGULATING G. | | | | | | | |
| ADENOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| DUODENUM | | | | | | | |
| ADENOCARCINOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| EPIDIDYMIDES | | | | | | | |
| LEIOMYOMA | 0 | 0 | 1 | 0 | 0 | 0.5909 | |
| MESOTHELIOMA | 0 | 1 | 1 | 1 | 0 | 0.6898 | 1.0000 |
| Mesothelioma/Leiomyoma | 0 | 1 | 2 | 1 | 0 | 0.7477 | 1.0000 |
| EYES | | | | | | | |
| SCHWANNOMA | 0 | 1 | 1 | 0 | 0 | 0.8559 | 1.0000 |

**Table A.3.3. (cont.) Tumorgenicity in Male Rats**

| Organ / Tumor | Con-troll | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| FEMUR INC JOINT | | | | | | | |
| HAEMANGIOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| H'POIETIC TUMOUR | | | | | | | |
| LYMPHOCYTIC/LYMPHOBLASTIC | 4 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| PLEOMORPHIC LYMPHOMA | 0 | 0 | 1 | 0 | 0 | 0.6007 | |
| HARDERIAN GLANDS | | | | | | | |
| ADENOMA | 0 | 1 | 1 | 0 | 0 | 0.8441 | 1.0000 |
| HEAD | | | | | | | |
| SEBACEOUS CELL CARCINOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| SEBACEOUS-SQUAMOUS CELL C | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| SQUAMOUS CELL CARCINOMA - | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| HEART | | | | | | | |
| ENDOCARDIAL SCHWANNOMA | 1 | 0 | 0 | 0 | 1 | 0.3542 | 0.5536 |
| ILEUM | | | | | | | |
| FIBROSARCOMA | 0 | 0 | 0 | 1 | 0 | 0.3812 | |
| MALIGNANT SCHWANNOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| JEJUNUM | | | | | | | |
| ADENOCARCINOMA | 2 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| KIDNEYS | | | | | | | |
| MALIGNANT SCHWANNOMA | 0 | 0 | 0 | 1 | 0 | 0.3966 | |
| LIVER | | | | | | | |
| HEPATOCELLULAR ADENOMA | 1 | 4 | 2 | 4 | 4 | 0.1925 | 0.3419 |
| HEPATOCELLULAR CARCINOMA | 0 | 0 | 0 | 0 | 2 | 0.0346 | 0.1072 |
| Hep. Adenoma/Carcinoma | 1 | 4 | 2 | 4 | 6 | 0.0382 | 0.0644 |
| LN AXILLARY | | | | | | | |
| HAEMANGIOMA | 0 | 0 | 0 | 1 | 0 | 0.3812 | |
| LN INGUINAL | | | | | | | |
| HAEMANGIOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| LN MESENTERIC | | | | | | | |
| HAEMANGIOMA | 9 | 12 | 8 | 9 | 2 | 0.9947 | 0.9965 |
| LYMPHANGIOMA | 2 | 3 | 0 | 1 | 0 | 0.9613 | 1.0000 |
| LUMBAR LN | | | | | | | |
| HAEMANGIOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| LUNGS & BRONCHI | | | | | | | |
| BRONCHIOLOALVEOLAR ADENOM | 3 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| MEDIASTINAL LN | | | | | | | |
| HAEMANGIOMA | 0 | 0 | 0 | 1 | 0 | 0.3846 | |
| MUSCLE | | | | | | | |
| FIBROSARCOMA | 0 | 0 | 0 | 0 | 1 | 0.1881 | 0.3304 |
| HAEMANGIOSARCOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| MALIGNANT SCHWANNOMA | 0 | 0 | 0 | 3 | 0 | 0.3972 | |
| NASAL TURBINATES | | | | | | | |
| OSTEOCHONDROMA | 0 | 0 | 0 | 0 | 1 | 0.2692 | 0.3333 |
| OSTEOMA | 0 | 0 | 0 | 0 | 1 | 0.1881 | 0.3304 |
| POLYPOID ADENOMA | 0 | 0 | 0 | 1 | 0 | 0.3812 | |
| OPTIC NERVES | | | | | | | |
| FIBROMA (MENINGEAL) | 0 | 0 | 1 | 0 | 0 | 0.6188 | |
| OROPHARYNX | | | | | | | |
| SQUAMOUS CELL PAPILLOMA | 0 | 1 | 0 | 1 | 2 | 0.0814 | 0.2573 |

**Table A.3.3. (cont.) Tumorgenicity in Male Rats**

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| PANCREAS | | | | | | | |
| ISLET CELL ADENOMA | 2 | 1 | 3 | 6 | 2 | 0.3971 | 0.5365 |
| ISLET CELL CARCINOMA | 0 | 0 | 1 | 0 | 1 | 0.1975 | 0.3304 |
| Islet Cell Adenoma/Carcin | 2 | 1 | 3 | 6 | 3 | 0.2256 | 0.3146 |
| MIXED CELL ADENOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| PARATHYROIDS | | | | | | | |
| CHIEF CELL ADENOMA | 2 | 4 | 3 | 4 | 2 | 0.6765 | 0.8260 |
| CHIEF CELL CARCINOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| PITUITARY | | | | | | | |
| ADENOMA - PARS DISTALIS | 23 | 20 | 19 | 18 | 20 | 0.5483 | 0.6024 |
| ADENOMA - PARS INTERMEDIA | 0 | 2 | 3 | 2 | 2 | 0.3264 | 0.3954 |
| Aden./Carc. Pars Dist./In | 24 | 22 | 23 | 22 | 22 | 0.5288 | 0.5717 |
| CARCINOMA - PARS DISTALIS | 0 | 0 | 1 | 2 | 1 | 0.1879 | 0.3304 |
| CARCINOMA - PARS INTERMED | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| PROSTATE | | | | | | | |
| ADENOCARCINOMA | 0 | 1 | 1 | 0 | 0 | 0.8512 | 1.0000 |
| ADENOMA | 3 | 1 | 1 | 3 | 0 | 0.8674 | 1.0000 |
| Adenoma/-carcinoma | 3 | 2 | 2 | 3 | 0 | 0.9287 | 1.0000 |
| RECTUM | | | | | | | |
| SARCOMA N.O.S. | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| SALIVARY GLANDS | | | | | | | |
| ADENOCARCINOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| ANAPLASTIC CARCINOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| MALIGNANT SCHWANNOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| SEMINAL VESICLES | | | | | | | |
| ADENOMA | 0 | 1 | 0 | 2 | 0 | 0.6176 | 1.0000 |
| CARCINOSARCOMA | 0 | 0 | 0 | 0 | 1 | 0.1911 | 0.3310 |
| SKELETAL MUSCLE | | | | | | | |
| GRANULAR CELL TUMOUR | 0 | 0 | 0 | 0 | 1 | 0.1881 | 0.3304 |
| SKIN | | | | | | | |
| FIBROMA | 0 | 0 | 0 | 0 | 1 | 0.1841 | 0.3246 |
| FIBROSARCOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| KERATOACANTHOMA | 3 | 1 | 1 | 1 | 2 | 0.4234 | 0.6379 |
| PILOMATRICOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| SEBACEOUS CELL ADENOMA | 0 | 0 | 0 | 1 | 0 | 0.3781 | |
| SQUAMOUS CELL PAPILLOMA | 1 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| TRICHOEPITHELIOMA | 1 | 0 | 2 | 0 | 0 | 0.8421 | 1.0000 |
| SPLEEN | | | | | | | |
| HAEMANGIOSARCOMA | 1 | 0 | 1 | 1 | 0 | 0.6794 | 1.0000 |
| SUBCUTIS | | | | | | | |
| ANAPLASTIC SARCOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| FIBROMA | 2 | 2 | 1 | 5 | 2 | 0.3668 | 0.6479 |
| LIPOMA | 0 | 0 | 1 | 1 | 0 | 0.4703 | |
| LIPOSARCOMA | 0 | 0 | 1 | 0 | 0 | 0.5909 | |
| MALIGNANT FIBROUS HISTIOC | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| MYXOSARCOMA | 0 | 0 | 0 | 0 | 1 | 0.1811 | 0.3165 |
| Systemic | | | | | | | |
| Hemangioma/-sarcoma | 10 | 15 | 9 | 11 | 2 | 0.9979 | 0.9990 |
| Schwannoma (incl. malig.) | 4 | 1 | 1 | 4 | 2 | 0.4980 | 0.7381 |

## Table A.3.3. (cont.) Tumorgenicity in Male Rats

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| TESTES | | | | | | | |
| INTERSTITIAL (LEYDIG) CEL | 1 | 3 | 2 | 1 | 2 | 0.4900 | 0.6489 |
| MESOTHELIOMA | 0 | 1 | 1 | 1 | 0 | 0.6898 | 1.0000 |
| THYMUS | | | | | | | |
| THYMIC CARCINOMA | 0 | 0 | 0 | 1 | 0 | 0.4008 | |
| THYMOMA (EPITHELIAL) | 0 | 0 | 1 | 0 | 0 | 0.5854 | |
| THYMOMA (LYMPHOID) | 3 | 1 | 1 | 2 | 0 | 0.8916 | 1.0000 |
| THYROIDS | | | | | | | |
| C-CELL ADENOMA | 9 | 7 | 12 | 6 | 9 | 0.5124 | 0.3852 |
| C-CELL CARCINOMA | 4 | 0 | 3 | 3 | 0 | 0.9110 | 1.0000 |
| C-Cell Adenoma/Carcinoma | 12 | 7 | 15 | 9 | 9 | 0.6939 | 0.5614 |
| FOLLICULAR CELL ADENOMA | 3 | 6 | 4 | 6 | 7 | 0.1360 | 0.1800 |
| FOLLICULAR CELL ADENOMA - | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| FOLLICULAR CELL CARCINOMA | 3 | 0 | 3 | 2 | 0 | 0.8935 | 1.0000 |
| Foll. Cell Adenoma/Carc. | 6 | 7 | 7 | 8 | 7 | 0.4168 | 0.4481 |
| TONGUE | | | | | | | |
| GRANULAR CELL TUMOUR | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |

## Table A.3.4. Tumorgenicity in Female Rats

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| ADIPOSE TISSUE | | | | | | | |
| LIPOMA | 0 | 0 | 0 | 1 | 1 | 0.1405 | 0.2679 |
| ADRENALS | | | | | | | |
| COMPLEX MEDULLARY TUMOUR | 0 | 0 | 1 | 0 | 0 | 0.6429 | |
| CORTICAL ADENOMA | 2 | 0 | 0 | 0 | 4 | 0.0287 | 0.1504 |
| PHAEOCHROMOCYTOMA | 2 | 2 | 1 | 0 | 1 | 0.6757 | 0.7966 |
| Phaeochromo./Med. Tumor | 2 | 2 | 2 | 0 | 1 | 0.7292 | 0.7966 |
| BONE | | | | | | | |
| HAEMANGIOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| BRAIN | | | | | | | |
| ASTROCYTOMA | 1 | 0 | 1 | 0 | 0 | 0.8214 | 1.0000 |
| GRANULAR CELL TUMOUR | 3 | 1 | 0 | 1 | 0 | 0.9308 | 1.0000 |
| HAEMANGIOMA | 0 | 0 | 0 | 0 | 1 | 0.1604 | 0.2679 |
| OLIGODENDROGLIOMA | 1 | 0 | 0 | 0 | 1 | 0.4133 | 0.6568 |
| PINEAL GLAND TUMOUR | 0 | 0 | 0 | 0 | 1 | 0.1604 | 0.2679 |
| CLITORAL GLAND | | | | | | | |
| ADENOMA | 0 | 1 | 1 | 0 | 0 | 0.8484 | 1.0000 |
| Adenoma/Carcinoma | 0 | 1 | 1 | 1 | 0 | 0.7160 | 1.0000 |
| CARCINOMA | 0 | 0 | 0 | 1 | 0 | 0.3955 | |
| DUODENUM | | | | | | | |
| FIBROMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| H'POIETIC TUMOUR | | | | | | | |
| LYMPHOCYTIC/LYMPHOBLASTIC | 0 | 1 | 0 | 2 | 1 | 0.2871 | 0.5611 |
| HEAD | | | | | | | |
| SQUAMOUS CELL CARCINOMA - | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| HEART | | | | | | | |
| ENDOCARDIAL SCHWANNOMA | 0 | 0 | 1 | 1 | 0 | 0.4035 | |
| HAEMANGIOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |

**Table A.3.4. (cont.) Tumorgenicity in Female Rats**

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| LIVER | | | | | | | |
| CHOLANGIOMA | 0 | 0 | 1 | 0 | 0 | 0.5615 | |
| HEPATOCELLULAR ADENOMA | 2 | 2 | 2 | 1 | 0 | 0.9096 | 1.0000 |
| HEPATOCELLULAR CARCINOMA | 1 | 0 | 1 | 2 | 1 | 0.2299 | 0.4657 |
| Hep. Adenoma/Carcinoma | 3 | 2 | 3 | 3 | 1 | 0.6947 | 0.8536 |
| LN MESENTERIC | | | | | | | |
| HAEMANGIOMA | 4 | 6 | 2 | 2 | 0 | 0.9830 | 1.0000 |
| LYMPHANGIOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| LUNGS & BRONCHI | | | | | | | |
| BRONCHIOLAR MUCINOUS ADEN | 0 | 0 | 0 | 0 | 1 | 0.1698 | 0.2857 |
| BRONCHIOLOALVEOLAR ADENOM | 1 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| Bronch. Muc./-alveolar Ad | 1 | 1 | 0 | 0 | 1 | 0.4207 | 0.6184 |
| MAMMARY AREA(S) | | | | | | | |
| Fibroma/-Adeno. | 13 | 20 | 13 | 14 | 17 | 0.2593 | 0.3313 |
| HAEMANGIOMA | 0 | 0 | 1 | 0 | 0 | 0.5615 | |
| MAMMARY ADENOCARCINOMA | 4 | 1 | 4 | 2 | 3 | 0.3666 | 0.4210 |
| MAMMARY ADENOMA | 0 | 2 | 0 | 1 | 0 | 0.7037 | 1.0000 |
| MAMMARY FIBROADENOMA | 10 | 15 | 11 | 10 | 13 | 0.3472 | 0.3506 |
| MAMMARY FIBROMA | 0 | 3 | 0 | 2 | 1 | 0.5164 | 0.8869 |
| MUSCLE | | | | | | | |
| FIBROMA | 0 | 0 | 0 | 0 | 1 | 0.1604 | 0.2679 |
| HAEMANGIOSARCOMA | 0 | 0 | 0 | 0 | 1 | 0.1604 | 0.2679 |
| NASAL TURBINATES | | | | | | | |
| POLYPOID ADENOMA | 0 | 0 | 1 | 0 | 1 | 0.1544 | 0.2679 |
| OROPHARYNX | | | | | | | |
| SQUAMOUS CELL CARCINOMA - | 0 | 0 | 0 | 0 | 1 | 0.2069 | 0.3396 |
| OVARIES | | | | | | | |
| CYSTADENOMA | 0 | 0 | 1 | 0 | 0 | 0.6627 | |
| GRANULOSA CELL TUMOUR | 1 | 4 | 3 | 5 | 3 | 0.3615 | 0.5249 |
| LUTEOMA | 0 | 0 | 0 | 0 | 1 | 0.1604 | 0.2679 |
| MALIGNANT GRANULOSA CELL | 0 | 0 | 0 | 1 | 0 | 0.5542 | |
| MALIGNANT SEX CORD-STROMA | 0 | 0 | 1 | 1 | 0 | 0.4035 | |
| MESOTHELIOMA | 0 | 0 | 0 | 0 | 1 | 0.1604 | 0.2679 |
| Ovarian tumors | 4 | 8 | 10 | 10 | 7 | 0.3270 | 0.2784 |
| SERTOLIFORM TUBULAR ADENO | 3 | 4 | 6 | 5 | 2 | 0.6353 | 0.7521 |
| SEX CORD-STROMAL TUMOUR | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| THECAL CELL TUMOUR | 0 | 0 | 0 | 0 | 1 | 0.3012 | 0.5312 |
| PARATHYROIDS | | | | | | | |
| CHIEF CELL ADENOMA | 1 | 1 | 0 | 1 | 0 | 0.7109 | 1.0000 |
| PITUITARY | | | | | | | |
| ADENOMA - PARS DISTALIS | 39 | 31 | 35 | 35 | 33 | 0.4325 | 0.5176 |
| ADENOMA - PARS INTERMEDIA | 3 | 2 | 2 | 4 | 4 | 0.1416 | 0.3258 |
| Adenoma/Carcinoma P. I./D | 42 | 38 | 43 | 43 | 40 | 0.3883 | 0.3642 |
| CARCINOMA - PARS DISTALIS | 2 | 6 | 6 | 6 | 5 | 0.3362 | 0.2868 |
| CARCINOMA - PARS INTERMED | 0 | 0 | 1 | 0 | 0 | 0.5951 | |
| Reproductive | | | | | | | |
| Schwannoma | 0 | 1 | 1 | 2 | 0 | 0.6076 | |
| SALIVARY GLANDS | | | | | | | |
| ADENOMA (PAROTID GLAND) | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |

**Table A.3.4. (cont.) Tumorgenicity in Female Rats**

| Organ / Tumor | Con-trol1 | Con-trol2 | Low | Med-ium | High | p-values: Trend | Hi vs Cntrl |
|---|---|---|---|---|---|---|---|
| SKIN | | | | | | | |
| BASAL CELL TUMOUR | 0 | 0 | 1 | 0 | 1 | 0.1544 | 0.2679 |
| BASOSEBACEOUS CELL TUMOUR | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| Baso./Basal Tumor | 1 | 0 | 1 | 0 | 1 | 0.3218 | 0.4657 |
| GRANULAR CELL TUMOUR | 0 | 0 | 0 | 0 | 1 | 0.3012 | 0.5312 |
| KERATOACANTHOMA | 0 | 0 | 1 | 0 | 0 | 0.5615 | |
| SQUAMOUS CELL PAPILLOMA | 1 | 0 | 1 | 0 | 0 | 0.8090 | 1.0000 |
| SPLEEN | | | | | | | |
| MESOTHELIOMA | 0 | 0 | 1 | 0 | 0 | 0.5615 | |
| STOMACH | | | | | | | |
| FIBROMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| SUBCUTIS | | | | | | | |
| FIBROMA | 1 | 2 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| FIBROSARCOMA | 0 | 1 | 1 | 0 | 0 | 0.8231 | 1.0000 |
| LIPOMA | 1 | 0 | 0 | 0 | 1 | 0.3327 | 0.5134 |
| SARCOMA N.O.S. | 0 | 0 | 0 | 1 | 0 | 0.3992 | |
| Systemic | | | | | | | |
| Hemangioma/-sarcoma | 5 | 7 | 3 | 2 | 2 | 0.9012 | 0.8920 |
| THYMUS | | | | | | | |
| MALIGNANT THYMOMA | 0 | 0 | 1 | 0 | 0 | 0.5591 | |
| THYMOMA (EPITHELIAL) | 2 | 0 | 2 | 0 | 0 | 0.9180 | 1.0000 |
| THYMOMA (LYMPHOID) | 4 | 7 | 5 | 0 | 2 | 0.9618 | 0.9290 |
| THYROIDS | | | | | | | |
| C-CELL ADENOMA | 7 | 5 | 9 | 3 | 10 | 0.1123 | 0.0920 |
| C-CELL CARCINOMA | 1 | 1 | 0 | 0 | 1 | 0.5152 | 0.7496 |
| C-Cell Adenoma/Carcinoma | 7 | 6 | 9 | 3 | 11 | 0.0892 | 0.0847 |
| FOLLICULAR CELL ADENOMA | 3 | 2 | 2 | 2 | 1 | 0.8438 | 0.9644 |
| FOLLICULAR CELL CARCINOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| Foll. Adenoma/Carcinoma | 3 | 3 | 2 | 2 | 1 | 0.8847 | 0.9742 |
| UTERINE CERVIX | | | | | | | |
| FIBROSARCOMA | 0 | 0 | 1 | 0 | 0 | 0.5615 | |
| MALIGNANT SCHWANNOMA | 0 | 0 | 1 | 0 | 0 | 0.6400 | |
| POLYP | 0 | 0 | 0 | 0 | 1 | 0.2040 | 0.3377 |
| UTERUS | | | | | | | |
| ANAPLASTIC CARCINOMA | 0 | 0 | 1 | 0 | 0 | 0.5755 | |
| DECIDUOMA | 0 | 0 | 1 | 1 | 0 | 0.4370 | |
| ENDOMETRIAL ADENOCARCINOM | 2 | 0 | 4 | 2 | 3 | 0.1967 | 0.1672 |
| ENDOMETRIAL ADENOMA | 0 | 1 | 0 | 1 | 0 | 0.5544 | 1.0000 |
| ENDOMETRIAL POLYP | 13 | 10 | 11 | 9 | 12 | 0.5469 | 0.6218 |
| End.Polyp/adenoma/deciduoma | 15 | 11 | 16 | 11 | 15 | 0.4173 | 0.3884 |
| GRANULAR CELL TUMOUR | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| LEIOMYOSARCOMA | 1 | 0 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| MALIGNANT SCHWANNOMA | 0 | 0 | 0 | 2 | 0 | 0.3590 | |
| VAGINA | | | | | | | |
| GRANULAR CELL TUMOUR | 0 | 0 | 0 | 0 | 1 | 0.1604 | 0.2679 |
| MALIGNANT SCHWANNOMA | 0 | 1 | 0 | 0 | 0 | 1.0000 | 1.0000 |
| Vagina/Cervix | | | | | | | |
| GRANULAR CELL TUMOUR | 0 | 1 | 0 | 0 | 1 | 0.2958 | |

## Appendix 4. References

Chu, K.C., Ceuto, C., and Ward, J.M. (1981), Fact s in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, *Journal of Toxicology and Environmental Health,* 8, 251-280

Haseman, J. K. (1983), A Reexamination of False-positive Rates for Carcinogenicity Studies, *Fundamental and Applied Toxicology,* 3, 334-339.

Lin, K. K. and Ali, M.W. (2006), Statistical Review and Evaluation of Animal Tumorigenicity Studies, *Statistics in the Pharmaceutical Industry,Third Edition,* edited by C.R. Buncher and J.Y. Tsay, Marcel Dekker, Inc. New York.

Lin, K. K. and Rahman, M.A. (1998), Overall False Positive Rates in Tests for Linear Trend in Tumor Incidence in Animal Carcinogenicity Studies of New Drugs, *Journal of Biopharmaceutical Statistics*. 8(1), 1-15.

Peto, R., Pike, M.C., Day, N.E., Gray, R.G., Lee, P.N., Parrish, S., Peto, J., Richards, S., and Wahrendorf, J. (1980). Guidelines for sample sensitive significance tests for carcinogenic effects in long-term animal experiments, *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, supplement 2: Long term and Short term Screening Assays for Carcinogens: A Critical Appraisal*, International Agency for Research Against Cancer, 311-426.

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
---
Steven Thomson
11/15/2006 09:42:39 AM
BIOMETRICS

Karl Lin
11/15/2006 10:06:32 AM
BIOMETRICS
Concur with review